RESISTANCE (EXERCISE) TRAINING IN NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE (CKD Stage 3) AND VALIDATION OF ULTRASOUND IN THE MEASUREMENT OF MUSCLE SIZE AND STRUCTURE IN HAEMODIALYSIS PATIENTS (CKD Stage 5)

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ABSTRACT

AIM: This thesis set out to make an original contribution to knowledge with regard to methods of assessing muscle size and architecture in the CKD and ESRD population, and to assess the ability to improve the muscle size and architecture, and symptoms of uraemia, by implementing an anabolic intervention (resistance exercise training) in the CKD population.

OUTCOME MEASURES: Ultrasound was shown to have high validity (against gold standard MRI measures; ICCs: VLACSA 0.96, VL depth 0.99, fat depth 0.98) and intra-rater reliability (ICCs: VL depth 0.98, total muscle depth 0.97, fat depth 0.99; MDC: VL depth 0.14cm, total muscle depth 0.19cm, fat depth 0.22cm) in measuring regional body composition at the mid-VL site in the CKD population.

There were significant ($p<0.01$) correlations between US-derived measures of (mid-VL) muscle size and architecture with strength and function (larger muscle mass and/or pennation angle positively correlated with higher strength and/or functional performance). Patient-reported uraemic symptoms were worse ($p<0.01$) in those with reduced strength and/or function.

INTERVENTION RESULTS: An anabolic (resistance training) intervention (12-weeks, randomized to once [RT1 n=7] or three times [RT3 n=10] per week, 80%1RM) brought about significant improvements over time ($p<0.01$) in all measures of muscle size and architecture (VL depth, total muscle depth, VLACSA, pennation angle). Interaction effects (group*time) were only seen in pennation angle ($p<0.05$) and VLACSA ($p<0.01$) where RT3 gains were greater than RT1 from week 8 onwards.

All measures of strength, function, and uraemic symptoms improved over time ($p<0.01$) with no interaction effects (no difference from greater training frequency/ volume).

CLINICAL AND RESEARCH IMPLICATIONS: The intervention results suggest implementing a RT form of "prehabilitation" in early stage (CKD3) patients just once per week is sufficient to bring about statistically and clinically important changes in strength and function that benefit the patient through reduced frequency and/or intrusiveness of uraemic symptoms (improved health-related quality of life), with minimal time-commitment.

Further research should examine if there is additional benefit to the significantly greater increases in VLACSA and pennation angle observed in RT3, with regards to long-term maintenance of functional improvements, and whether an RT1 or RT3 programme delays the progression of CKD, the need for RRT, and patient mortality.

Key words

Chronic kidney disease, pre-dialysis, non-dialysis dependent

Ultrasound, ultrasonography, B-mode

Resistance exercise, training, rehabilitation, prehabilitation

Strength, Function, Body composition, uraemic symptoms, health-related quality of life

Muscle architecture, pennation angle, anatomical cross-sectional area, vastus lateralis

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(CA) PD	(Continuous ambulatory) peritoneal dialysis
(e) GFR	(estimated) Glomerular filtration rate
(HR) QoL	(Health-related) Quality of life
(M) HD	(Maintenance) Haemodialysis
(P) RT	(Progressive) Resistance Training
1-RM	1- repetition maximum
ACSA	Anatomical cross-sectional area
ADL	Activities of daily living
BIA	Bioelectrical impedance analysis
BMI	body mass index
C-F	capillary-to-fibre ratio
CKD	Chronic Kidney Disease
CRF	Chronic renal failure
CVD	Cardiovascular disease
ESRD	End-stage renal disease
FFM	Fat-free mass
FM	Fat mass
Hb	Haemoglobin

KEPF	Knee extension peak force
LPPF	Leg press peak force
LUSS	Leicester Uraemic symptom score
MAC	Mid-arm circumference
MRI	Magnetic resonance imaging
MTC	Mid-thigh circumference
NDD	Non-dialysis dependent
NHS	National Health Service
PAR	Physical activity recall
PCSA	Physiological cross-sectional area
PEW	Protein-energy wasting
RRT	Renal replacement therapy
SGA	Subjective global assessment
STS	Sit-to-stand
US	Ultrasound
VL	vastus lateralis muscle

CHAPTER 1 - Introduction

Chronic Kidney Disease (CKD) is an important public health issue. It is a common and progressive disease, and the prevalence increases with age (2012 UK Renal Registry annual report, 2013), which means that the disease burden will increase with our ageing population. Chronic kidney disease is an independent risk factor for other diseases, particularly cardiovascular disease (USRDS, 2013 Annual Report; Shastri & Sarnak 2010). In a minority of cases, chronic kidney disease progresses to end stage renal disease (ESRD), which may require renal replacement therapy (RRT) (Eriksen & Ingebretsen 2006; 2012 UK Renal Registry annual report, 2013). This progression and the risks of other vascular events, such as stroke and heart failure, can be reduced if chronic kidney disease is identified and well-managed (NICE clinical guidelines 73, 2008). Therefore early diagnosis is essential.

A UK population study estimated that in people with CKD there was a 4% risk of progression to end stage renal disease (ESRD) over a 5.5 year follow-up period (Drey et al 2003). ESRD is a long-term irreversible decline in kidney function, for which renal replacement therapy (RRT) is required if the individual is to survive (NHS Kidney Care, 2010).

The incidence of RRT (new patients on RRT per year) in the UK was approximately 108 per million population (0.01%) in 2012, an increase from 95 per million in 2001, with total numbers (prevalence) undergoing RRT much greater still (an increase to 861 from 523 per million population in 2000; 0.09% total prevalence; 2012 UK Renal Registry annual report, 2013).

The increased incidence and prevalence may be in part due to earlier diagnosis, increased awareness, and the fact the population as a whole is living longer, with Chronic Kidney Disease often associated with older age groups (average transfer to RRT

was 64.6 years old; 2012 UK Renal Registry annual report, 2013). Whatever the reason, there are more individuals needing a greater healthcare provision, and because of this, there is an increased burden on the NHS.

Disproportionate to the one-tenth of a percent of the UK population undergoing RRT, at least 2% of the NHS budget is spent on renal replacement therapy per annum (UK renal registry annual report, 2013). This is massively unbalanced, and non-medical interventions are being investigated to reduce the impact of renal disease on both the individual patients, and the NHS purse (Ansell et al 2006). Evidently more patients are presenting with the need to transfer to RRT, and more are living longer once on RRT, but the cost to the NHS is disproportionately large.

CKD manifests in many ways, with frailty and disability a major consequence of the generalised wasting observed in the population (Johansen et al 2013). Often dietary restrictions are imposed on CKD patients to reduce the stress on the kidneys (Goraya & Wesson 2012). Alongside this, as the disease progresses other uraemic symptoms and hormonal changes bring about loss of appetite and fatigue, further contributing to the progressive atrophy, protein energy wasting, weakness, and frailty (Kim et al 2013).

CKD patients that have been defined as frail are started on dialysis on average much earlier (i.e. at a higher estimated glomerular filtration rate, eGFR) than those deemed non-frail (Johansen et al 2013), and sadly the deterioration trajectory is amplified from dialysis initiation, as higher levels of dependence in performing activities of daily living (ADLs) are recorded in these frail patients (Johansen et al 2013). Additionally, although dialysis reverses uraemia, the procedure itself alongside the residual metabolic imbalances, inflammation, and comorbid conditions, may allow protein energy wasting to develop further (Carrero et al. 2013), leading to a loss of muscle mass beyond normal physiological muscle wasting (Fahal 2013; Pupim et al 2005).

Thesis Aim 1 [Chapter 4]

Explore the effect of CKD stage on body composition, strength and function in different stages of CKD (early and late stage) using standard clinical and frailty outcome measures.

To be able to fully assess the extent of wasting in chronic kidney disease, and to later evaluate the ability of an intervention to bring about change, it is essential that an accurate record can be made of patients' body composition at different stages of the disease trajectory/progression, at both the group and individual level. Many studies assessing body composition in chronic wasting diseases have enlisted the use of highly specific and accurate equipment such as Magnetic Resonance Imaging (MRI; Bemben et al 2002), dual-energy x-ray absorptiometry (DEXA; Nielsen et al 1994; Emmons et al 2011), or Computed Tomography (CT)-scans (Thomaes et al 2012; Noorkoiv et al 2010a). These methods are the gold standard in body composition assessment, but come at a high price both in efficiency and financially, and are not ideal for large population intervention studies.

Other common methods to attempt to detail change in body composition include near-bedside methods that can be implemented without disturbing the patient too much (unlike the gold standard methods), at relatively low cost to the research or clinical team undertaking the measurements, and with easy-use instructions. Those currently in use include anthropometric measures such as waist, leg, or arm girth (circumference) (Carvalho et al 2012; Chang et al 2011), waist-to-hip ratio (Emmons et al 2011; Elsayed et al 2008), body mass index (Ishihara et al 2010; Catalano et al 2008), skinfold assessment (Chang et al 2011; Khan et al 2009), bioelectrical impedance analysis (Avesani et al 2001, Bellizzi et al 2006), and clinician-led subjective global assessment scores (Dong et al 2011; Steiber et al 2004).

Useful though these are for data-collection in large population studies where individual differences are lost to the group average, they are not accurate or specific enough to track or assess an individual at any one point. These methods are largely unable to differentiate between muscle and fat (girth measures, body mass index [BMI], subjective global assessment [SGA]), and those that can (skinfold measures, bioelectrical impedance analysis [BIA]) are highly prone to error in repeated measures, especially in a populations prone to highly variable hydration status, such as CKD. To truly be able to assess the size of the effect from any given intervention within an individual and a larger group is vital.

Ultrasound measures of body composition have been used in non-CKD populations to assess muscle and fat depths (English et al 2012a; Trip et al 2009), cross-sectional area (Narici & Cerretelli 1998; Bamman et al 2000; Matschke et al 2010a), and muscle volume (Thomaes et al 2012; Martins et al 2007). As with the near-bedside methods, ultrasound is minimally invasive to the patients and highly portable. Ultrasound also has the added benefit of being able to assess muscle architecture (e Lima et al 2012; Bleakney & Maffulli 2002).

Thesis Aim 2 [Chapter 5]

Aim 2a: evaluate the validity of ultrasound compared to a gold standard measure (MRI) of body composition in CKD patients.

Aim 2b: establish the reproducibility of ultrasound measurement of regional body composition (muscle and fat depths), with a view to assessing its utility as a method of monitoring change in CKD patients.

Late presentation of ESRD (where RRT is necessary within 90 days of diagnosis) has reduced from 23.9% in 2006 to 19.3% in 2012 (UK renal registry annual report, 2013), once again likely due to an increased awareness of CKD amongst non-nephrologists, and the introduction of estimated GFR reporting. In fact, most recent reporting

demonstrates that the majority (two-thirds) of CKD incident patients presented at least 12 months before they needed to start RRT (2012 UK Renal Registry annual report, 2013); ultimately leading to a greater number of patients spending longer in the pre-dialysis period than ever before.

It is important to emphasize that both uraemia and sarcopenia (loss of muscle mass and strength) are progressive diseases. Uraemia is a clinical syndrome associated with fluid, metabolic abnormalities, electrolyte and hormone imbalances which develop in parallel with deterioration of renal function. Some of these abnormalities start earlier in the course of the uraemia and others appear late (Fahal et al 2013; Kovesdy et al 2013).

Examining the body composition of patients earlier in the disease process (pre-dialysis) has been done before, using gold standard techniques such as DEXA (Nielsen et al 1994), or others (BIA: Avesani et al 2001, Bellizzi et al 2006, Carvalho et al 2012), but mainly anthropometrics and skinfolds (Castaneda-Sceppa et al 2007, Chang et al 2007, Carvalho et al 2012). Assessing muscle size and quality in pre-dialysis patients using ultrasound is therefore important to establish the extent of wasting prior to the need for RRT.

Thesis Aim 3 [Chapter 6]

To explore, in pre-dialysis CKD patients, the relationship between ultrasound-derived estimates of regional body composition (muscle and fat depth, and muscle architecture), and routinely employed measures for the assessment of body composition, physical function, and uraemic state, at this point in the disease trajectory.

Ultimately the CKD population is seeking an intervention or rehabilitation programme which increases lean body mass, strength, function, health-related quality of life, and

reduces the level of exertional fatigue for the patient, alongside improved mortality and reduced hospitalization. The intervention should also hinder the progression of the disease.

Non-medical interventions to prevent or hinder protein energy wasting, decline in muscle mass and strength, and consequent development into worsening frailty and disability have been investigated in the ESRD (RRT/dialysis) population. Using a variety of anabolic interventions in different combinations of nutritional supplementation (Jadeja & Kher 2012; Ikizler 2009), steroids, growth hormone, or testosterone (Johansen et al 1999; 2006; MacDonald et al 2007) and exercise (Cheema et al 2011; Oliveros et al 2011; Chen et al 2010) among others, has offered mixed results in these late-stage CKD patients, with similar interventions often reporting no change or only minor or not clinically significant improvements in body composition, clinical measures, strength, and function (Segura-Orti et al 2009; Headley et al 2002; Cheema et al 2011).

Most studies focus on haemodialysis patients, despite this sub-group making up only a small fraction of patients with CKD (Perlman et al 2005). Stages 2-4 are pre-dialysis, and make up the majority of patients with the disease. Ideally, anabolic interventions such as exercise training should begin as soon as possible, commencing in the pre-dialytic stage, where exercise benefits are potentially greater and more prolonged, allowing significant improvements throughout the varying stages of the disease progression. Fitts et al (1999) found that exercise coaching and counselling was more beneficial in pre-dialysis patients than for those already undergoing dialysis, suggesting that before CKD patients approach the dialysis stage of treatment, a pre-habilitation intervention could maintain and aid recovery of physical capacity.

A review of exercise interventions in CKD (Howden et al 2012) determined that introducing a programme of supervised resistance training to the non/pre-dialysis population may improve muscle function and strength, mobility and walking distance, and reduce inflammation. In the catabolic state where muscle wasting is common,

resistance training may prevent reduction in skeletal muscle mass, and improve muscle mass and function.

Thesis Aim 4 [Chapter 7]

To evaluate the effects of frequency of a resistance training programme in patients with stage 3 CKD.

Sub-aims of RT intervention [Chapter 7]

- Measure and compare any change in muscle size or architecture brought about by the different frequencies (once or three times per week) of the RT programme.
- Assess and compare any change from the RT programme in strength and ADL-related function, as well as reported patient-uraemic symptoms.

CHAPTER 2 - Literature Review

2.1 Chronic Kidney Disease (CKD)

2.1.1 Prevalence and Progression

Over three million people face chronic kidney disease in the UK today; and this number is expected to rise over the next ten years. Meanwhile, an estimated 13,000 people are killed by the disease annually in this country (Kidney Research UK, 2013). Over 2% of the total NHS budget is spent on renal replacement therapy (dialysis and transplantation) for those with established renal failure (Ansell et al 2006). Strategies aimed at earlier identification and (where possible) prevention of progression to established renal failure are therefore clearly required (NICE guidelines, 2008).

The standard definition or criteria for a diagnosis of CKD is either (1) Kidney damage for three-months or longer; structural or functional abnormalities of the kidney, or (2) Glomerular Filtration Rate (GFR) less than 60mL/min/1.73m^2 for three-months or longer, with or without kidney damage (KDOQI Guidelines, 2000).

Chronic kidney disease (CKD) is a progressive condition, and patients are classified according to their degree of renal failure and hence the severity of the disease. To determine at which stage an individual is presenting, the glomerular filtration rate (GFR) is measured. The GFR is a measure of how quickly the kidneys are cleaning the blood, and is reported in millilitres per minute (mL/min). A normal/healthy GFR is greater than 90 mL/min. Table 2.1 describes the various stages of chronic kidney disease (CKD) and the corresponding GFR.

In Stages 1 and 2 CKD, there are often few symptoms. If CKD is identified at this stage, medication and lifestyle changes can slow down the disease progression and

potentially stop or reverse CKD depending on the initial cause. In CKD stage three (CKD3), anaemia may develop and should be treated immediately. When CKD has progressed to stage four (CKD4), preparations for dialysis or kidney transplant will be made.

Table 2.1 - Stages of chronic kidney disease (CKD)

Stage	Description	GFR	Percentage of UK population*
0	"Normal kidney function" Healthy kidneys	≥ 90 mL/min	64.2
Stage 1	Kidney damage with normal or high GFR	≥ 90 mL/min	23.0
Stage 2	Kidney damage and mild decrease in GFR	60 – 89 mL/min	7.3
Stage 3a	Moderate decrease in GFR	45 – 59 mL/min	4.5
Stage 3b		30 – 44 mL/min	0.7
Stage 4	Severe decrease in GFR	15 – 29 mL/min	0.1
Stage 5	Established renal failure (ERF) End-stage renal disease (ESRD)	≤ 15 mL/min or on dialysis	0.0

**Percentage data taken from britishrenal.org, FAQ 2010*

CKD5 (CKD stage 5) is also known as end-stage renal disease (ESRD) and is the final stage of the disease-process. The clinical features of ESRD are described in Table 2.2. By this stage, the only options are usually a form of renal replacement therapy (RRT), whether by maintenance dialysis or a kidney transplant.

For about 40% of adults on dialysis a kidney transplant is the treatment of choice, though this percentage is higher in children. If patients do not have a kidney transplant, dialysis is needed for the rest of the patient's life. Two main types of dialysis are available, haemodialysis (HD) and peritoneal dialysis (PD).

At any one time in the UK, 400–800 people per million of the population need renal replacement in the form of dialysis (NICE guidelines, 2011). The prevalence of dialysis in the UK is highly age dependent; for adults aged 70–80 years it is between 1600 and 2000 people per million (NICE guidelines, 2011).

Table 2.2 – Clinical features of end-stage renal disease (ESRD)

Musculoskeletal System	• Myopathy and muscle weakness • Bone pain and radiographic findings (renal osteo-dystrophy)
Respiratory System	• Tachypnea • Dyspnea (lung oedema) • Pleural effusion
Renal System	• Small kidneys • Nocturia (urination at night) • Oligura (<400ml/day) or polyuria (>2.5L/day)
Haematologic System	• Anaemia • Bleeding tendency • Low resistance to infection
Neurological symptoms	• Depressed mental functions • Somnolence (drowsiness) • Peripheral neuropathy
Skin and Mucosae	• Peri-oral “uraemic frost” • Pruritus (itching)
Cardiovascular System	• Hypertensive heart disease • Arrhythmia • Pericarditis • Increased jugular venous pressure
Gastrointestinal System	• Nausea • Anorexia • Vomiting

2.1.2 Co-morbidities

Many chronic kidney disease patients may have one or more co-morbidities; a disease or condition that exists alongside another disease. The most common co-morbidities in CKD patients are diabetes and hypertension, but also include cardiovascular disease (CVD), congestive heart failure, lung disease, peripheral vascular disease, neurological problems, and malnutrition. Some of the most common ailments and co-morbidities linked with CKD are detailed below.

2.1.2.1 Cardiovascular Disease (CVD)

People with CKD are at increased risk of cardiovascular disease (CVD), and this is the number one cause of death due to complications as CKD progresses to ESRD (Go et al 2004). Cardiovascular disease is present in 63% of patients with advanced CKD, compared with 5.8% of adults without CKD (USRDS, 2009 Annual Report). Patients with CKD are more likely to die from cardiovascular events than progress to dialysis, and cardiovascular events account for 45% of deaths in dialysis patients (Shastri & Sarnak 2010). Prevention and treatment of cardiovascular disease in CKD involves addressing traditional cardiovascular risk factors, including hypertension, dyslipidemia, diabetes, anaemia and other metabolic abnormalities.

2.1.2.2 Hypertension (high blood pressure)

The prevalence of hypertension is 84% in patients with stage 4–5 CKD, compared with 23% of adults without CKD (USRDS, 2009 Annual Report). Additionally, up to 75% of CKD patients have blood pressure levels above 140/90 mmHg (Chobanian et al 2003). Hypertension is associated with accelerated progression of kidney disease as well as development and worsening of cardiovascular disease.

2.1.2.3 Diabetes

Diabetes mellitus increases the likelihood of CKD and risk of cardiovascular events and death in patients with CKD. Patients with stage 3–5 kidney disease have an increased risk of hypoglycemia (low blood sugar) due to decreased medication clearance and

impaired kidney gluconeogenesis (generation of glucose from non-carbohydrate substrates) (KDOQI 2007).

2.1.2.4 Hyperkalaemia (high blood potassium)

Normal serum potassium levels are 3.5-5.0 mmol/L. High blood potassium (>5.5 mmol/L) is common in CKD patients, with more severe disease stages and diabetes increasing the frequency and severity of hyperkalaemia (Einhorn et al 2009). Hyperkalaemia can also develop due to consuming large amounts of potassium in the diet, acidosis, hyperglycaemia in diabetic patients, and some medications.

2.1.1.5 Anaemia

Anaemia can be diagnosed at any stage of CKD but is more common in patients with more severe CKD and becomes especially prominent in patients with stage 4–5 CKD (USRDS, 2009 Annual Report). Anaemia can result from iron deficiency, B_{12} and folate deficiency, and relative erythropoietin deficiency in CKD. However, anaemia does not appear to worsen over time, or it may respond to iron supplementation/therapy.

2.2 Demographics of muscle wasting and physical impairment in CKD

Patients with chronic kidney disease (CKD) are characterized by a profound decrease in muscle mass or atrophy, in particular at end-stage (stages 4-5) (Kouidi et al 1998). The causes of this are multi-factorial in origin, though the generalized muscle wasting is strongly associated with a decline in functional capacity and strength that is directly linked with a greater risk of morbidity and mortality (Kopple et al 2005).

The issue of poor physical performance and functioning in patients on dialysis has been noted and been under sporadic investigation for some time, following the publication of an article highlighting the physical activity and rehabilitation status of haemodialysis patients (Gutman et al 1981). Early indications seemed to suggest it was the level of

anaemia that restricted an individual's ability and capacity for exercise, activities of daily living, and general function. However, later reports showed the level of performance remained low even after one year's treatment with recombinant human erythropoietin introduced to combat the anaemia associated with renal failure (Ifudu et al 1994).

The weakness has also in part been attributed to water and electrolyte disturbances, cardiac failure, malnutrition, carnitine deficiency, physical inactivity, comorbidities such as ischaemic heart disease, and age-related issues such as sarcopenia and other disabilities (reviewed by Fahal 2013). As an individual approaches end stage renal disease (ESRD), exercise tolerance worsens and even high functioning ESRD patients display a poorer level of physical performance when matched to persons with comparable chronic disorders such as heart failure and chronic obstructive pulmonary disease (COPD).

There is little to no difference between haemodialysis patients and controls in excitation-contraction coupling, central activation, and specific tension when expressed as a ratio of maximal voluntary strength to contractile cross-sectional area (Johansen et al 2003, Fahal et al 1997), strongly indicating that the biggest cause for muscle weakness and consequent poor function and performance is muscle atrophy. The observed muscle fibre and contractile area atrophy is greater than in healthy controls, even when corrected for the different habitual activity level (Johansen et al 2003).

2.3 Protein Energy Wasting and Cachexia in CKD

Patients with chronic kidney disease (CKD) frequently exhibit substantial atrophy of skeletal muscle which is often associated with protein-energy wasting. Protein-energy wasting (PEW) refers to the nutritional and catabolic alterations that occur in CKD. A

reduced appetite and dietary restrictions often contribute to the wasting (insufficient calorie intake/under-nutrition), but other factors are necessary for PEW to fully develop (Bonanni et al. 2011), including inflammation and increased energy expenditure due to uraemia (Fried et al. 2006), comorbid conditions associated with chronic disease (low levels of physical activity, frailty), and additionally the effect of the dialysis procedure itself in CKD stage 5 (Carrero et al. 2013).

In the most severe cases of PEW, it is referred to as cachexia (Fouque et al. 2008). Cachexia is highly prevalent in moderate to severe cases of CKD, including up to 75% of patients undergoing maintenance haemodialysis (Mak et al. 2011). Therapies against muscle wasting during non-CKD specific cachexia have often concentrated on increased food intake, or by "normalising" the metabolic changes within the patient, however, cachectic patients often fail to adapt to excess protein stores and consequently persist in a state of negative nitrogen balance, that cannot be corrected with nutritional intervention alone (Ebner et al. 2013).

PEW naturally develops with the progression of CKD, and is an inherent component of advanced disease. Although dialysis reverses uraemia, the dialysis procedure itself alongside the residual metabolic derangements, inflammation, and comorbid conditions may allow PEW to develop or worsen (Carrero et al. 2013), leading to a loss of muscle mass beyond normal physiological muscle wasting (Fahal 2013).

2.4 Frailty in CKD

Frailty has previously been defined as a biological syndrome of decreased reserve and resistance to stressors that results from cumulative declines across multiple physiologic systems, and causes vulnerability to adverse outcomes (Kim et al. 2013). Currently it is assessed/diagnosed according to the presence of three or more of the following

criteria: unintentional weight loss (10lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity (Fried et al. 2001).

Frailty is observably more common in individuals with CKD than those without (Johansen et al. 2013) and frailty in moderate to severe CKD was more common than in other chronic illnesses, such as vascular disease, cancer and other degenerative diseases of ageing (Wilhelm-Leen et al. 2009). Risk of frailty is increased by approximately 2-times in mild CKD (stages 1-3a), and 6-times in moderate to severe (stages 3b-5) CKD (Wilhelm-Leen et al. 2009) and is associated with increased incidence of adverse outcome in dialysis patients (increased hospitalization, increased death rate; Johansen et al 2013; Kosmadakis et al 2010).

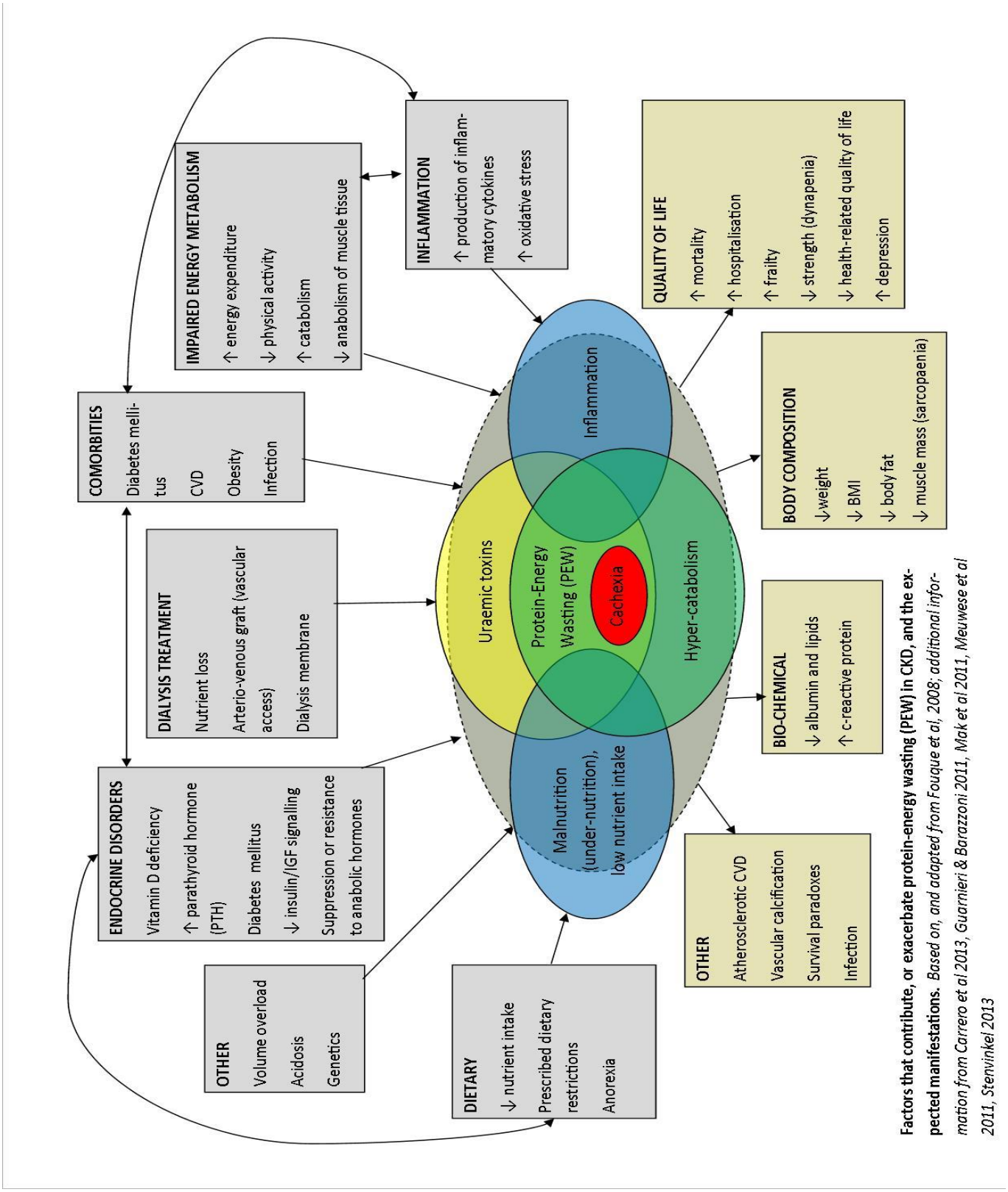
CKD patients that have been defined as frail are started on dialysis on average much earlier (i.e. at a higher estimated glomerular filtration rate, eGFR) than those deemed non-frail (Johansen et al 2013) and sadly the deterioration trajectory continues to accelerate, even with the initiation of dialysis, as higher levels of dependence in performing activities of daily living (ADLs) are recorded in these patients (Johansen et al. 2013).

This underscores the need to intervene as early as possible in the disease trajectory of CKD patients with a view to slowing the descent into “frailty”. This would hopefully delay these patients being put onto maintenance dialysis and protect their independence for longer (Johansen et al 2013).

Figure 2.1 shows the multitude of factors that contribute, or exacerbate protein-energy wasting (PEW) in CKD, and the expected manifestations. The most important of these outcomes to the patient is likely to be their health-related quality of life. Of the factors

contributing to the milieu, few can be modified or adapted to attempt to relieve some of the negative outcomes. These few include reduced anabolism of muscle tissue, physical activity levels, nutritional intake and deficiencies and co-morbidities such as obesity.

Figure 2.1 – Factors that contribute to protein energy wasting and consequent frailty



Factors that contribute, or exacerbate protein-energy wasting (PEW) in CKD, and the expected manifestations. *Based on, and adapted from Fouque et al, 2008; additional information from Carrero et al 2013, Guarnieri & Barazzoni 2011, Mak et al 2011, Meuwese et al 2011, Stenvinkel 2013*

2.5 Mechanisms of muscle protein gain and loss

The balance of muscle protein synthesis and degradation is vital to maintaining the lean body mass of an individual. Muscular hypertrophy exists when synthesis is greater than degradation, and atrophy occurs in the reverse circumstances. Muscle wasting can therefore be due to reduced rate of protein synthesis, or increased breakdown, or more commonly a combination of both. After a great deal of research in recent years, it has become established that anabolism (process of construction or synthesis using energy) is not simply the reverse of catabolism (process of breakdown or degradation releasing energy), but instead a number of interactions exist between them (Glass 2005).

Contributing factors to increased degradation and reduced synthesis of protein include the direct and individual effect of advancing age, sedentary behaviour, poor nutrition, androgen deficiency, oxidative stress, metabolic acidosis, and insulin resistance. Inflammation also appears to up-regulate the release of hormones (ubiquitin-proteasome pathway) that contribute to muscular atrophy (reviewed by Johansen 2009). The treatment for CKD and the disease itself could alter the protein balance, as studies in rats (Du et al 2004) and later patients with ESRD (Workeneh et al 2006) demonstrated an increase in hormonal (caspase-3) activity in uraemic environments. However, correction of acidosis in pre-dialysis (Reaich et al 1993), peritoneal dialysis (Graham et al 1996) and haemodialysis patients (Graham et al 1997) has shown a reduction of protein degradation in all three groups, though a similar decrease in protein synthesis was also seen.

Improving the anabolic pathway appears to be the popular and most common therapeutic method to date and include nutritional interventions (dietary supplementation, or using amino acid dialysate), anabolic hormone therapy (growth hormone therapy, or androgen treatment), and exercise (resistance) training.

2.6 Body composition in CKD

Body composition in CKD has been strongly associated with level of dependence, frailty and mortality. Low adiposity (within a healthy range) in the healthy population is generally linked with greater health outcomes (BMI 18.5-25kg/m^2 and waist circumference men <102cm, women <88cm, lower risk of all-cause mortality in adults >60 years old; Sui et al 2007). However, in the renal disease cohort, increased BMI has shown beneficial links with life expectancy and disease status up to the highest BMI category (>40; Kalantar-Zadeh 2005), this paradoxical relationship has also been noted in cholesterol levels and blood pressure (Nishizawa et al 2006).

This has been referred to in the literature as the "obesity paradox" or "reverse epidemiology" (Park et al 2014; Speakman & Westerterp 2010; Schmidt et al 1999). It is possible that the increased survival rate in CKD with greater BMI is more due to the greater absolute volume of fat-free (lean) mass than fat mass in weightier patients. However in a study comparing HD patients over a period of 4-5 years, overall mortality (cardiovascular risk) was not predicted by fat-free (lean) mass, but instead by fat mass, independent of other confounding factors (Nishizawa et al 2006).

This paradox has been seen to revert back to the norm following renal transplantation (Schold et al 2007), suggesting that it is a true biological phenomenon (Speakman & Westerterp 2010). This in itself presents a problem, as questions arise as to whether end-stage renal patients should be encouraged to lose weight in preparation for transplant, or maintain a higher BMI to retain the protective obesity paradox in the event of continued dialysis. Additionally, for those patients not yet on dialysis, the dilemma is whether they should be advised to attempt to increase their BMI for a potential risk reduction, or indeed reduce it to a "healthy" BMI to reduce the negative

effects as seen in “original epidemiology” (the obesity paradox is also apparent in CKD patient populations who are not on dialysis; Kovesdy & Anderson 2007).

2.6.1 Regional body composition in CKD

Patients with CKD often suffer with co-morbidities such as diabetes and CVD, with the latter being the biggest cause of death in the renal population (risk of CVD death is 10-30 times greater than in the general population; Levey et al 1998).

In non-diabetic, non-dialysis CKD patients, the independent factor for insulin resistance is the amount of total body fat (Satirapoj et al 2005). However, the relationship between fat mass and inflammatory biomarkers appear to differ between truncal and non-truncal fat mass (Axelsson et al 2004). Truncal fat mass is closely related to visceral fat which has previously been identified as a key factor in the development of insulin resistance, type II diabetes, premature atherosclerosis, and CVD (Lafontan & Berlan 2003; Arner 2003).

Reduced central (truncal or intra-peritoneal) adiposity is of particular importance as truncal fat mass releases two to three times the volume of inflammatory cytokines than non-truncal fat mass (Fried et al 1998), which are associated with increased morbidity and mortality (Cordeiro et al 2010; Postorino et al 2011). Though a recent study (Yuan et al 2013) has suggested that despite the increased production and release of serum hepatocyte growth factor (HGF, inflammatory cytokine) in patients with greater truncal fat mass, it may not be fully detrimental in the CKD5 (dialysis) population, as HGF attenuates the inflammatory response, and through the suppression of inflammation it can protect from oxidative damage (Shimizu et al 2012).

Total protein loss due to wasting can be very high; approximately two-thirds of which is skeletal muscle (chronic and critical illness, Monk et al 1996; Streat & Hill 1987; Reid et al 2004). In a healthy population, immobility/inactivity alone leads to massive reductions in appendicular strength and skeletal muscle, with the antigravity muscles (calf and back) deteriorating at an accelerated rate than the non-postural muscles such as grip strength (Bloomfield 1997, Geboers et al 2000).

Due to the increased in truncal adiposity, variable subcutaneous fat, and in particular the appendicular (skeletal muscle) wasting, measurement and monitoring of regional body composition is important in the CKD population to further explain the reverse epidemiology/ obesity paradox and truly assess the effect of interventions to assist the patient.

2.6.2 Methods of body composition assessment

Management and measurement of regional body composition is of vital importance in the CKD population. Therefore an effective method of assessment is necessary to be able to track and monitor changes in body composition in CKD patients. Simply using a BMI value can be helpful but is not ideal as it cannot differentiate between lean (fat-free) tissue and fat mass. However some measurement tools that can differentiate between the different tissues are available and have previously been implemented to assess body composition as a one-off measure or repeated for interventions or longitudinal studies.

2.6.2.1 Gold Standard Assessments:

2.6.2.1.1 Dual-Energy X-ray Absorptiometry (DXA/DEXA)

Initially used to examine bone density in osteoporosis, DEXA can give clear and accurate imaging assessments of the whole body in other chronic diseases and a

variety of sports activities to evaluate the effects of exercise, muscle atrophy and hypertrophy. DEXA uses a three compartment model to account for variation in bone mineral content. It has been validated against a four compartment model, which includes body water calculated by isotopic deuterium dilution, across a varied population (Prior et al 1997). However, despite the reduction in scanning time in recent years (Andreoli et al 2009), the general lack of portability limits the use of DEXA in research in restricted spaces and on multiple sites.

2.6.2.1.2 Computed Tomography (CT)

For measurements of subcutaneous fat, computed tomography is seen as the gold standard as the process can distinguish between subcutaneous and visceral fat which can be of great importance in the diagnosis and tracking of certain metabolic disorders and illness. Limitations include high ionizing radiation (x-rays) levels, financial cost, and relative immobility (Orphanidou 1994), making it unsuitable for repeated measures and near-bedside/field experiments.

2.6.2.1.3 Magnetic Resonance Imaging (MRI)

For standard imaging of muscle size, MRI scans are often used due to the high quality of information produced. Once again, the limited availability and relative cost (time, fiscal) is high and less feasible for regular repeated measures on a broad and numbered subject group.

2.6.2.1.4 Muscle Biopsy

In conditions that are associated with muscle atrophy and hypertrophy, the gold standard for muscle filament size and number, as well as cell content, is by muscle biopsy. A highly invasive procedure, often leaving the patient in unnecessary pain, it is often unfeasible for regular repeated measures, especially in a frail, elderly, and ill population. Site selection will influence size of adipocytes (deep sites are smaller than

subcutaneous fat cells; Brodie 1988) and assumptions on cell number based on size will vary.

2.6.2.2 Anthropometry and other methods of assessment:

2.6.2.2.1 BMI, waist or limb circumference, and waist-to-hip ratio

Body mass index (BMI), waist circumference, and waist-to-hip ratio are indirect anthropometrical indices commonly used in large epidemiological studies into obesity, health status, and generalized nutritional studies in adults. They are simple, cheap, standardized and ideal for mass use in a normal or average population.

BMI is the ratio of body weight to height (weight in kg/height in metres^2). Waist circumference and waist-to-hip ratio are simple girth measurements. Measurements in this way have been useful predictors of cardiovascular and all-cause mortality in young adults. However, simple measurement error such as poor posture (height measure), bowel status (weight), holding breath (waist circumference), or bad placement of the tape measure (for waist or limb circumference) will elicit an inaccurate reading.

These methods cannot differentiate between fat mass (FM) and fat free mass (FFM), and thus do not allow for the greater muscle mass in well trained individuals, or indeed the sarcopaenic effect of ageing, for example, a reduction in FFM and increased FM, decrease in height, repositioning of fat from peripheral areas to central, and loss of gluteal muscle bulk (Gallagher et al 2000; Roubenoff & Hughes 2000).

2.6.2.2.2 Skinfold thickness measurements

Skinfold thickness uses a two-component model, which assumes that there is a fixed proportion of water, protein, and mineral in FFM, despite their variation between individuals, and are influenced by age, gender, ethnicity, genetics, diet, and exercise. From a technical angle, skinfold caliper operators require extensive training and

practice and even the most skilled technician can vary site location, skin selection, and pinch between measures. Clearly this method only measures subcutaneous fat (fat below the skin) and is less accurate for very lean/thin or obese subjects.

2.6.2.2.3 Underwater/ hydrostatic weighing (hydro-densitometry)

Underwater weighing (also a two-component model like skinfold thickness), though relatively accurate and consistent (good for assessing changes in body fat) the process can be uncomfortable for the subject (full submersion), time consuming, with equipment very cumbersome and lacks mobility in the same way as MRI, CT, and DEXA.

2.6.2.2.4 Urine analysis – 24hr creatinine levels, and 3-methylhistidine excretion

Urine sampling has previously been used to measure the level of skeletal muscle loss (levels of either creatinine or 3-methylhistidine within a sample) following different modes and intensities of exercise; studying the effect of muscle breakdown with acute, chronic, eccentric, aerobic forms of exercise. Protein loss in chronically ill patients is particularly notable in renal disease, and it is often used to initially diagnose the condition.

Exercise (increased protein breakdown) can lead to increased markers in urine if inadequate dietary protein is available to replace stores (nothing available for synthesis; Campbell et al 2002). A fall over time in urinary nitrogen can be due to increased retention of nitrogen in the body from the onset of a resistance training (RT) intervention (Campbell et al 2002); the shift in urinary nitrogen excretion reflects a training-induced conservation of body nitrogen (favouring protein synthesis and anabolism; Campbell et al 1995).

After a creatinine controlled diet (meat-free), a complete 24-hour urine sample is collected and analysed for creatinine content. An alternative is to use plasma or serum

creatinine. It is directly proportional to total body muscle mass, however it is time-consuming (24-hour collection), can be awkward for the subject, dietary restriction needs to be employed before each collection, and there can be daily variation in creatinine excretion (Lemann & Doumas 1987).

An alternative excretory product found in urine is 3-methylhistidine (3MH), it is proportional to total muscle mass, and has strong correlations with total body potassium and FFM (Brodie 1988). However, 24-hour urine collection is still necessary along with a meat-free/controlled diet (Wang et al 1998).

2.6.2.2.5 Total body potassium (TBK)

Potassium (K) is a measureable element *in vivo*, and the use of total body potassium (TBK) as an index of body composition has a long history in nutritional research. Body potassium is distributed entirely in the fat-free mass (FFM) compartment, and a large proportion exists in skeletal muscle mass (~60% of TBK in skeletal muscle, Wang et al 2003). TBK provides an estimate of body cell mass, the metabolically active lean tissue of the body, and is often considered the reference value for the assessment of true lean mass (Corcoran et al 2000). The determination of TBK is based on the fact that the proportion of total potassium found in human tissues as ^{40}K is constant at 0.0118% of total potassium (Burmeister 1965; Forbes & Hursch 1961). Therefore, by measuring ^{40}K it is possible to calculate total-body potassium. As potassium is distributed almost entirely within the intracellular compartment of fat-free mass, and using the ratio of total-body potassium to fat-free mass, once TBK is known it is possible to calculate fat-free mass and total-body fat.

The test procedure requires the participant to lie still on a bed which passes under the detectors. The participant must first be shielded from naturally occurring radiation in the environment, using concrete, lead or steel. Once the external radiation is

minimized, the subject's natural radiation as ^{40}K (potassium) is measured through the use of scintillation counters. The radiated ^{40}K is measured over a specified time period and from this TBK is estimated; these detectors count the naturally occurring radioactive emissions from the potassium (K) in the body.

As with DEXA, CT and MRI, this method of body composition assessment requires highly sensitive and expensive equipment, with limited availability. The equipment is not easily accessible and restrictions exist for any participants having undergone any radioactive medical procedures in the previous week (e.g. X-rays, CT scans, mammograms, or radiotherapy).

2.6.2.2.6 Bioelectrical Impedance Analysis (BIA)

BIA measures the body's resistance to flow (impedance) of alternating electrical current at a designated frequency between points of contact on the body. The conductive nature of water in body tissue allows measurement of body impedance, indirectly providing information regarding the tissue content; highly conductive tissue (intracellular and extracellular water; ICW ~55%, ECW ~45%, summed to total body water, TBW), and less conductive tissue (high resistance; adipose/body fat).

Single-frequency BIA phase angle and impedance are measured at 50kHz. Reactance and resistance can be calculated precisely at this current, and is inversely related to extracellular fluid content, fat, or excess fluid (Piccoli & Codognotto 2004, Piccoli et al 2005, Pillon et al 2004). Some devices report an estimation of lean mass from these figures, though should be interpreted cautiously, and are likely not valid in a renal dialysis population where excess fluid is common (Tattersall 2009). Multiple-frequency BIA measures reactance and resistance at multiple frequencies (5-1000kHz) to differentiate between extracellular (frequency 0kHz) and intracellular fluid (extrapolated "infinite" kHz measures extracellular and intracellular) (Cole & Cole

1941), allowing estimations of lean and adipose mass (most fluid in adipose is extracellular, and most fluid in lean tissue is intracellular).

BIA is portable, simple to use, quick, cheap and has no subject height or weight restrictions. It is a useful tool for clinical studies using repeated measures to monitor progress, but may be less suitable for large (cross-sectional) epidemiological studies with diverse population unless validated in different environments (higher skin temperature decreases impedance; Gudivaka et al 1996), and specific populations (ethnicity, disease-state) (Dehghan & Merchant 2008). BIA is not a measure of muscle quality, but instead of quantity.

Typically whole-body BIA analysis has required single electrodes positioned on the dorsal surface of the foot, ankle, wrist, and hand on one side of the body, but it has been suggested that using these four single-site electrodes can cause error in repeated TBW measurements (Moon et al 2009). By fixing the distance between electrodes (distance 5cm between wrist site and hand site and 5cm between ankle and foot site; Moon et al 2010; Cornish et al 1999; Kyle et al 2004; haemodialysis patients; Kaysen et al 2005) this reproducibility error can be reduced (for repeated measures). However, small errors could be clinically insignificant as BIA could not detect a change in TBW of 1.4% in a 70kg reference man (Elsen et al 1987). Often seen as a more accurate method of measurement, it has previously been suggested that the need for constant and consistent hydration status between measures can greatly limit the power and significance of the results (Campbell et al 1995).

Whole body BIA assessment rests on the assumption that the body is one large cylinder with the same resistivity throughout. This does not allow for the relative impact of the trunk which contributes little to resistance (~10%) but contains a large conductor volume (~50%; Lukaski et al 1986). For larger individuals, or those with unusual body

mass distribution, segmental BIA is more suited, overcoming these large assumptions by separating the legs, arms, and trunk and altering the respective resistance for each (Organ et al 1994). Segmental multi frequency BIA has shown body fat percentage deviations in validation (Shafer et al 2009) against a gold standard (DEXA) by 1.56% (underestimate in normal weight), 0.58% (overweight), and 3.4% (obese), demonstrating increasing inaccuracies with increasing adiposity (Deurenberg 1996); however, the biological significance is considered small and within the precision of the BIA and DEXA instruments (2%) (Shafer et al 2009).

BIA has been shown to have high inter-rater reproducibility on repeated measures (Segal et al 1991) and has been highly correlated with hydrostatic weighing, DEXA and isotopic deuterium dilution techniques in a number of populations (healthy; Basile et al 2008, healthy lean to obese; Anderson et al 2012, haemodialysis; Dou et al 2011, healthy children and adults; Erceg et al 2010, Jensky-Squires et al 2008, breast cancer; Gupta et al 2008, lung cancer; Gupta et al 2009, elderly hyponatraemic; Hoyle et al 2011). Errors could arise from the possible inaccurate measurement of resistance in the body torso, suggested through the greater inaccuracies found with greater central adiposity (36% variation attributed to waist circumference; Shafer et al 2009).

Phase Angle (a direct measurement from BIA with no need for height and weight information) has been shown to have significantly and consistently high sensitivity and specificity with three standardized nutritional assessments and screening tools routinely used worldwide to categorize hospital admissions and chronic patients (Nutritional Risk Screening Tool 2002, Kondrup et al 2003, Subjective Global Assessment questionnaire, and Albumin levels, Kyle et al 2012). Phase angle also correlated significantly with FFM in controls and patients. Generally, a low phase angle (below 5° in men, 4.6° in women; Kyle et al 2012, over 5.4 normal, 4.5-5.4 borderline, under 4.4 abnormal; Selberg & Selberg 2002) is representative of poor nutritional

status, with phase angles between 4.5 and 5.6° associated with short-term survival in cancer patients (Gupta et al 2004, Toso et al 2000). Elderly patients with phase angle below 3.5° had four times the hospital mortality than those between 5.0-5.5° (Wirth et al 2010).

The biological meaning of phase angle is not entirely understood but it is considered a strong indicator for cell health (high phase angle, better cell function). The smaller phase angle seen in otherwise healthy elderly participants (Kyle et al 2012) reflects their general reduction in physical function and health (Barbosa-Silva et al 2005) alongside reduced skeletal muscle mass (and therefore intracellular water, possibly influenced further by oedema). Patients in rehabilitation programmes have improved phase angle when compared to seriously ill patients but still lower than healthy age-matched controls (Gunn et al 2008). Higher phase angle has been noted with greater maximal quadriceps strength (Gunn et al 2008).

There have been recent suggestions of utilizing BIA in predictions of VO_2max without exercise testing. Stahn et al (2008) assessed 115 healthy individuals of varying weight and fitness level, and found strong correlations between intracellular resistance and VO_2max ($r=0.89$), significantly superior to predictions based on anthropometry. The group concluded this model (using BIA) is most appropriate (and with the highest level of accuracy) for subjects with relatively low ($<2.5 L min^{-1}$) aerobic fitness levels, though currently do not recommend use in clinical settings.

2.6.2.2.6.1 BIA use in chronic and critical illness

Segmental multi-frequency BIA is appealing to use clinically to assess an ill or diseased population because of the potential to assess fluid distribution (Steijaert et al 1997). Dialysis must control the body's fluid accurately to maintain optimal health; however, many tools currently used to assess fluid removal are imprecise and excessive fluid

removal carries immediate health risks. Current controls in place are monitoring blood pressure, body weight, and changes in blood volume but these can be affected by a number of medications such as anti-hypertensives.

Optimal or normal fluid content can be estimated from height, weight, and body fat percentage using multi-frequency BIA, then subtracting this value from total body fluid content (from BIA), the excess fluid can be estimated (Chamney et al 2002, Moissl et al 2006). Multiple-frequency segmental BIA can be used to calculate excess fluid volume to within 1-2 litres (Tattersall 2009) and in nutritional assessment as an objective measure of body composition.

Given a specific population reference range, it is possible to assess hydration status using a standard nomogram using resistance and reactance (scaled for height). This is possible with a whole body single-frequency BIA model (Piccoli et al 2004, Piccoli et al 2005, Pillon et al 2004) or pricier whole body multiple-frequency (Lopot et al 2002, Lindley et al 2005, Katzarski et al 1996). Segmental multi-frequency BIA can account for fluid shifts within the body (between segments) possibly caused by change in posture such as during or after dialysis. Fluid shifts and changes in body composition have also been observed using BIA in elective surgical cardiac patients (CABG) post-operatively (Feyrer et al 2003).

A recent study group (Nakao et al 2007) used multi-frequency BIA to establish a Body Protein Index (BPI) to evaluate whole body somatic protein stores as a potential new marker to assess nutritional status in chronic renal failure and patients on maintenance dialysis. This successfully highlighted that patients with a longer dialysis history showed a tendency to lower BPI compared to those with a shorter history, despite no difference in age.

2.6.2.2.7 Ultrasound (US)

With the development and increased prevalence of wasting diseases worldwide it has become necessary to use techniques of investigation which procure lower costs through efficiency of application and validity of measures. Easily accessible and cheap (often used) measures with low training requirements, such as mid-thigh circumference (MTC), have been shown to have low correlation with generalised FFM (Campbell et al 1995). Clearly there is a need for a more accurate measurement of muscle and fat. High resolution ultrasonography has been used internationally for subcutaneous scans and research as it is non-invasive and requires no prerequisites for the patient (stability in status, level of cognition; Bemben 2002; Whittaker & Stokes 2011).

In recent years, muscle imaging has called upon the use of brightness (B)-mode ultrasonography. Originally used to measure fat deposits and skin folds in animal husbandry, B-mode ultrasound been adopted by researchers seeking to accurately measure muscle thickness and localised muscle cross-sectional area in humans. Equipment is inexpensive in comparison to other clinical methods such as MRI or DEXA, and can be taken to the patient at their bedside, in a research laboratory, or other non-clinical site. Examples of ultrasound use in the measurement and assessment of body composition is shown in Table 2.3 in other (non-CKD) populations.

High resolution ultrasound (US) has shown great potential as an alternative (near-bedside/patient) method to assess muscle and fat mass at specific anatomical sites; it has been shown to accurately measure change in muscle size resulting from anabolic interventions and also to monitor the effects of ageing and disuse in a variety of populations though most were healthy and of working age (knee-joint injury, Uremović et al 2004; healthy men, Miyatani et al 2002; Miyatani et al 2004; healthy adults and patients with multiple organ failure, Campbell et al 1995; older men and women,

Bemben 2002; critically ill hemiplegic, Moukas 2002; working age healthy, Sanada et al 2006; healthy adults, Ahtiainen et al 2010).

Table 2.3 - Studies using Ultrasound to assess body composition (non-CKD) (grouped by study design and ordered alphabetically by author)

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
COMPARATIVE AND CROSS-SECTIONAL STUDIES														
Abe et al 2011 Journal of Geriatric Physical Therapy 34 (4): 168-73	inactive elderly	comparative (young vs old women)	8 sites: anterior and posterior	B-mode US 5 MHz	elderly: 157F 67.9±6.3yrs (range 60-85yrs) height 149±5cm weight 52.2±6.5kg BMI 23.6±2.6 young: 152F 25.3±4.3yrs (range 20-34yrs) Height 158±5cm Weight 52±5.2kg BMI 20.7±2.1			bicep brachii MTH/limblength mm/cm		0.81 ± 0.14				<0.001
								triceps brachii MTH/limblength mm/cm		0.84 ± 0.19				0.273 (ns)
								abdomen MTH/height cm/m		0.51 ± 0.11				<0.001
								subscapula MTH/height cm/m		1.16 ± 0.26				0.004
								quadriceps MTH/limblength mm/cm		0.98 ± 0.19				<0.001
								hamstrings MTH/limblength mm/cm		1.52 ± 0.18				<0.001
								triceps surae MTH/limblength mm/cm		1.65 ± 0.16				0.032
								tibialis anterior MTH/limblength mm/cm		0.70 ± 0.08				0.105 (ns)

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
COMPARATIVE AND CROSS-SECTIONAL STUDIES														
Birtles et al 2002	chronic exertional compartment syndrome	comparative (healthy vs patients)	anterior tibial muscle	B-mode US	Exp: 20 (14M) Age 27.6 ± 4.7yrs Weight 85.8 ± 10.7kg BMI 27.7 ± 3.6	isometric exercise of AT group	1 session	muscle thickness mm	28.7 ± 1.0	31.0 ± 1.1		8	<0.05	ns
Med Sci Sports Exerc 34 (12): 1900-6				7.5 MHz and 5-10 MHz	Con (healthy): 22M 33 ± 10.4yrs Weight 72.6±10.4kg BMI 23.3±2.8									
Bleakney & Maffulli 2002	intramedullary nailing	self-controlled (compared to healthy leg)	quadriceps	8cm linear array	13 Age 43.2years Range 16-82yrs	immobilisation		VL pennation angle		15.4 range 10-21				0.0002
J Sports Med and Phs Fitness 42 (1): 120-5		cross-sectional		7.5 MHz				VL muscle fibre length mm		64.9 range 56-78				0.002
		(2 patients longitudinal)						rectus femoris ACSA cm2		3.7 range 0.8-8.0				0.0004
								anterior MTH of quadriceps mm		24.4 range 14-33				0.001
Hakkinen et al 2005	rheumatoid arthritis	comparative (women with RA vs healthy)	thigh	convex trans-ducer	patients: 21F 44±9yrs (range 32-56yrs) Height 165±6cm Weight 63.7±13.4kg	combined strength and aerobic	21 weeks	quadriceps femoris MTH cm	4.75 ± 0.65		0.35	7.4	<0.001	0.81 (ns)
Clin Exp Rheumatol 23 (4): 505-12				5MHz	healthy: 12F 42±9yrs (range 32-56yrs) Height 163±5cm Weight 62.6±6.8kg		3 session every 2weeks	subcutaneous fat cm	3.08 ± 1.41		-0.38	-12.3	<0.001	0.10 (ns)

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
COMPARATIVE AND CROSS-SECTIONAL STUDIES														
Kubo et al 2007	elderly men	comparative study	knee extensors and plantar flexors	B-mode US	elderly: 17M 70.4±4.8yrs			knee extensor MTH mm		29.8 ± 5.3				<0.001
Journal of Gerontology 62a (11): 1252-8				7.5 MHz	Height 159.7±6.7cm Weight 59.7±8.7kg			KE MTH/thigh length mm/cm		0.81 ± 0.15				<0.001
					young: 19M 26.4±3.7yrs			plantar flexor MTH mm		62.7 ± 6.9				<0.001
					Height 171.4.8cm Weight 71.8±11.8kg			PF MTH/thigh length mm/cm		1.78 ± 0.19				ns
Matschke et al 2010a	cachectic with rheumatoid arthritis	comparative (wasted RA vs healthy)	vastus lateralis		RA: 14 (3M, 11F) 61.6±3.3yrs (range 22-72yrs)			VL PCSA cm2		31.3 SEM 2.3			0.07 (ns)	
J Rheumatol 37 (2): 282-4					healthy: 14 (3M, 11F)			pennation angle		8.5 SEM 0.4			0.07 (ns)	
					62.2±3.5yrs (range 22-76yrs)			VL volume cm3		391.2 SEM 21.4			0.01	
Matschke et al 2010b	rheumatoid arthritis	comparative study	quadriceps	7.5 MHz linear probe	RA: 23 (7M,16F) 60 SEM 2 yrs (range 22-72yrs)			VL PCSA cm2		34.2 ± 1.9				<0.05
Med Sci Sports Exerc 42 (12): 2149-55					Height 165±1cm weight 75.5±3.1kg			VL pennation angle at rest		8.85 ± 0.3				<0.05
					healthy: 23 (7M, 16F) 60 SEM 3 yrs (range 22-76yrs)			VL pennation angle at contraction		11.7 ± 0.5				ns
					Height 168±2cm Weight 73.6±2.6kg			VL fascicle length at rest cm		13.4 ± 0.5				0.06 (ns)
								VL fascicle length at contraction cm		11.3 ± 0.6				ns

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
COMPARATIVE AND CROSS-SECTIONAL STUDIES														
da Silva et al 2012a Respir Care 57 (4): 572-82	exercise induced bronchospasms (EIB) in obese	comparative (EIB vs nonEIB)	visceral and subcut fat		EIB: 15 (12F,3M) 16±1yrs Height 170±0cm Weight 99±18kg Con (Non EIB): 20 (12F,8M) 17±1.6yrs height 170±10cm weight 102±13kg	weight loss programme - nutrition, psychological, and physical interventions	one year 3times/ wk	visceral fat cm subcutaneous fat cm	3.8 ± 0.9 4.0 ± 1.1	2.0 ± 0.7 3.0 ± 0.7	-1.7 ± 1.0 -0.9 ± 1.1		<0.001 <0.001	ns ns
da Silva et al 2012b Pediatric Pulmonology 47: 8-17	asthmatic obese	comparative (asthmatic vs non-asthmatic)	visceral and subcut fat		asthmatics: 26 (20F,6M) 16±1.1yrs Height 170±10cm Weight 112±19kg non-asthmatics: 50 (33F,17M) 17±1.4yrs Height 168±10cm Weight 101±15kg	weight loss programme - nutrition, psychological, and physical interventions	one year 3times/ wk	visceral fat cm subcutaneous fat cm	4.2 ± 1.4 3.9 ± 0.9	2.5 ± 0.9 3.0 ± 0.8			<0.05 ns	
Young et al 1982 Clinical Science 62: 227-34	knee injury	self controlled (compared to healthy leg)	quadriceps		14 (10, 4) Age (median) 25years Age (range) 19-44yrs			non wasted quadriceps ACSA cm2 male non wasted quadriceps ACSA cm2 female non wasted quad fibre area um2 male non wasted quad fibre area um2 female		80.0 range 64-89 52.8 range 43-57 4669 range 3370-7400 3411 range 2780-4100				

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
LONGITUDINAL/ PROSPECTIVE COHORT														
Gruther et al 2008 J Rehabil Med 40: 185-9	critically ill	longitudinal	quadriceps	high resolution real-time US	17 (14M, 3F) 55±17yrs Height 174±12cm Weight 84±21kg		28 days	quadriceps femoris MTH		-ve correlation with length of stay			<0.01	
Uremovic et al 2004 Coll Antropol 28 suppl 2: 227-33	knee joint injury	longitudinal Self-controlled: injured leg vs healthy leg	m. quadriceps	7.5 MHz linear probe	patients: 30 (21m, 9f) 30.6±10.3yrs Weight 74.6±12.8kg Height 173±6.8cm control: 30 30.2± 6.9yrs Weight 71±8.5kg Height 172.5±6.2cm	physical rehab after immobilisation	6 weeks	rectus femoris volume mm3 vastus intermedius volume mm3	13953 ± 2812 13234 ± 2736	15688 ± 3487 14936 ± 2555			<0.001 <0.001	<0.01 <0.001
CASE STUDY														
Reid et al 2008 Critical Care 12 (3): R79	critically ill - Addison's disease	case study	bicep brachii, forearm, thigh		1F 38 years old ICU stay 33days Admission weight 69kg BMI 25.3 Discharge weight ↓11.2kg, ↓16.2%	"intensive physical rehab" and "nutrient-dense nutritional support regimen"	12 months	body mass and fat mass lean mass		regained body mass due to body fat increases	+2.5kg after discharge		ns	

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
NON-RANDOMISED CONTROLLED TRIALS														
Gibson et al 1988 The Lancet , October pp767-70	simple distal third fracture of tibia immobilisation (in cast)	nonRCT	quadriceps	grey-scale US 3.5 MHz	exp: 7m age 26yrs (range 18-49yrs) con: 14m age 48yrs range 19-76yrs	electrical muscle stimulation	6 -7 weeks 1 hr/day	quadriceps CSA cm2	53.3 ± 11.3	50.9 ± 9.0			<0.05	
Kawakami et al 2001 European Journal of Applied Physiology 84: 7-12	healthy men	nonRCT	quadriceps	B-mode US 7.5 MHz	9 Ex: 5, Con: 4 Age range 18-28yrs Height 172 ± 4.6cm Weight 68.4 ± 10.6kg	immobilsation (head down bed rest) isometric exercise (leg extension)	20 days	TRAINED pennation angle UNTRAINED pennation angle	17.7 ± 2.3 19.8 ± 3.9	17.6 ± 1.8 19.5 ± 4.1		-0.2 ± 4.4 -1.4 ± 2.8		
Moukas et al 2002 Clinical Nutrition 21(4): 297-302	critically ill hemiplegic	nonRCT	hemiplegic upper arm	M-mode US 10 MHz linear array high res	37 (23m, 14f) 58 ± 13yrs	immobilsation and drug therapy	4 days measured on day 1 and 10	all patients muscle mass cm	2.49 ± 0.59	1.99 ± 0.51	- 0.49 ± 0.20	- 20.09 ± 6.83	<0.001	

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
UNCONTROLLED TRIALS														
Abe et al 1997	healthy	uncontrolled	9 sites: anterior and posterior	B-mode US	8 (4, 4)	bed rest	20 days	anterior foream MTH mm	19.8 SE 1.4	19.3 SE 1.4		-2.5		
J Gravitat Physiol 4(1): s10-14					Age 20.9 ± 1.7yrs			anterior upper arm MTH mm	24.8 SE 2.0	25.1 SE 2.2		1.2		
					Height 169.5 ± 6.5 cm			posterior upper arm MTH mm	31.5 SE 1.8	30.9 SE 1.8		-1.9		
								abdomen MTH mm	13.3 SE 0.8	14.4 SE 0.7		8.3	<0.05	
								subscapular MTH mm	19.3 SE 1.2	17.8 SE 1.1		-7.8	<0.05	
								anterior thigh MTH mm	52.8 SE 2.0	50.5 SE 1.9		-4.4		
								posterior thigh MTH mm	57.6 SE 2.5	56.4 SE 2.5		-2.1		
								anterior leg MTH mm	29.3 SE 1.9	28.6 SE 1.9		-2.4		
								posterior leg MTH mm	65.4 SE 2.2	63.3 SE 2.2		-3.2	<0.05	
Galvao et al 2006	prostate cancer	uncontrolled	upper arm, thigh	B-mode US	10M 70.3±8.3ys (range 59-82yrs)	PRT	20 weeks	bicep brachii MTH cm	2.69 ± 0.54	2.91 ± 0.57		3.5 ± 6.9	ns	
Med Sci Sports Exerc 38 (12): 2045-52				5 MHz	Weight 80.2±10.9kg BMI 27.4±3.3		twice/ week	tricep brachii MTH cm	1.94 ± 0.26	2.33 ± 0.49		5.5 ± 17.0	ns	
								quadriceps MTH cm	2.15 ± 0.30	2.46 ± 0.41		15.7 ± 12.1	0.05	
								hamstrings MTH cm	4.52 ± 0.74	4.53 ± 0.89		0.2 ± 10.0	ns	

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
RANDOMISED CONTROLLED TRIALS														
Bernardes et al 2012 Sao Paulo Medical Journal 130 (1): 5-9	pelvic organ prolapse	RCT	levator ani muscle	2-D transperineal US 4-7MHz	Exp ("group2"): 21 56.7±10.7yrs BMI 28.8±3.9 Con ("group3"): 16 58.7±10.4yrs BMI 29.7±2.7	pelvic floor muscle training and hypopressive exercises	12 weeks	CSA muscle cm2	1.4 ± 0.3	1.8 ± 0.5			0.001	
Candow et al 2008 Med Sci Sports Exerc 40 (9): 1645-52	healthy elderly men	RCT	elbow, knee, ankle flexors and extensors	B-mode US	C+P: 10M 67.3±3.1yrs Weight 82.5±2.8kg Height 177.2±2.1cm	RT with creatine +protein,	10 weeks	muscle thickness cm CP (creatine protein)						
					Cr: 13M 65.5±2.7yrs Weight 86±5.4kg Height 175.4±2.3cm	RT with creatine alone	3times/ wk	elbow flexor	2.9 ± 0.2	3.1 ± 0.2		9.0 ± 6	<0.05	
								elbow extensor	4.3 ± 0.3	4.7 ± 0.3		11.6 ± 5	<0.05	
					Con (pla): 12M 64.1±3.1yrs Weight 82.9±2.9kg Height 178.3±1.3cm	RT + placebo		knee flexor	4.9 ± 0.3	5.2 ± 0.2		7.0 ± 5.2	<0.05	
								knee extensor	3.3 ± 0.3	3.8 ± 0.3		13.6 ± 4.7	<0.05	
								ankle plantar flexors	3.8 ± 0.3	4.3 ± 0.2		14.1 ± 5.0	<0.05	
								ankle dorsi flexors	2.3 ± 0.1	2.5 ± 0.3		4.6 ± 5.1	ns	
								combined mth				10 ± 5.2		<0.05

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
RANDOMISED CONTROLLED TRIALS														
								Cr (creatine only)						
Candow et al 2008	*continued*	*from previous*	*page*					elbow flexor	2.8 ± 0.2	3.0 ± 0.2		8.8 ± 3.7	<0.05	
								elbow extensor	4.1 ± 0.2	4.5 ± 0.2		11.4 ± 4.3	<0.05	
								knee flexor	4.5 ± 0.2	4.8 ± 0.2		9.4 ± 3.6	<0.05	
								knee extensor	3.3 ± 0.2	3.6 ± 0.2		11.3 ± 3.7	<0.05	
								ankle plantar flexors	3.5 ± 0.2	3.9 ± 0.3		13.8 ± 4	<0.05	
								ankle dorsi flexors	2.1 ± 0.1	2.3 ± 0.2		7.9 ± 6.7	ns	
								combined mth				10.4 ± 4.3		<0.05
Cornish et al 2009	healthy untrained >60yrs	RCT	elbow and knee extensors and flexors	B-mode US	51 65.4±0.8yrs	PRT with/out nutritional supplementation	12 weeks	FEMALE elbow flexor MTH cm	2.9 ± 0.7	3.2 ± 0.7			<0.01	
Applied Physiology, Nutrition and				5MHz	placebo: 14m, 12f		3days/ week	FEMALE elbow extensor MTH cm	3.7 ± 1.3	4.6 ± 0.7			<0.01	
Metabolism 34 (1): 49-59					supplement group: 14m, 11f			FEMALE knee flexor MTH cm	5.1 ± 1.7	5.1 ± 1.7				<0.05
								FEMALE knee extensor MTH cm	3.5 ± 0.7	4.0 ± 0.7			<0.01	
								MALE elbow flexor MTH cm	3.6 ± 0.4	4.0 ± 0.7			<0.01	
								MALE elbow extensor MTH cm	4.4 ± 1.1	5.2 ± 1.1			<0.01	
								MALE knee flexor MTH cm	5.2 ± 1.5	6.1 ± 1.1				<0.05
								MALE knee extensor MTH cm	3.4 ± 0.4	3.4 ± 0.4			<0.01	

Table 2.3 (continued) – US to assess body composition

Author, year, journal	population type	study design	Area/ body-site investigated	US used	Participant number n (m,f) and further details	intervention details	time/ duration	Mode of assessment (US site/measure)	pre intervention (baseline values)	post intervention values	actual change reported	% change if reported	(p)-value	group difference (p)
RANDOMISED CONTROLLED TRIALS														
Gerovasili et al 2009	critically ill	RCT	quadriceps	GE Vivid 7 US	exp: 13 (6M,7F) 59±23yrs	electrical muscle stimulation of quadriceps and peroneous longus muscles	2-9days after admission	right rectus femoris cross-sectional diameter cm	1.42 ± 0.48	1.31 ± 0.45	- 0.11 ± 0.06	-8 ± 3.9	0.001	<0.05
Critical Care 13 (5): R161				7.5 MHz	con: 13 (8M,5F) 56±19yrs		55 mins/ day	right vastus intermedius cross sectional diameter cm	0.91 ± 0.39	0.81 ± 0.38	-0.10 ± 0.05	-12.5 ± 7.4	0.001	<0.05
Gruther et al 2010	critically ill (ICU) - acute and long term	RCT	knee extensors	high resolution real-time	stimulation group acute patients: 8 (7M,1F)	neuromuscular electrical stimulation	4 weeks	ACUTE PATIENTS quadriceps femoris (vastus intermedius and rectus femoris) MTH	28.9 ± 6.6	18.3 ± 3.2	-10.6	-36.7	0.02	ns
J Rehabil Med 42: 593-7					stimulation group longterm patients: 8 (7M,1F) control acute: 9 (8,1) control longterm: 8 (4,4) Total: 55±15yrs		5times/ wk	LONGTERM PATIENTS quadriceps femoris (vastus intermedius and rectus femoris) MTH	18.4 ± 4.2	19.3 ± 3.8	0.09	4.9	0.036	0.013

Presented as mean ± standard deviation unless otherwise stated; IQR = interquartile range; SEM = standard error of the mean; SE = standard error; RCT = randomised controlled trial; nonRCT = non randomised controlled trial; Xover = crossover design; exp = experimental group; co/con = control group; pla = placebo group; MTH = muscle thickness; VL = vastus lateralis; CSA = cross sectional area; PRT = progressive resistance training; 2-D = 2-dimensional; US = ultrasound or ultrasonography; ns = non-significant result

Ultrasound imaging produces a two-dimensional view based on transmission and reflection of high-frequency waves in a given plane. This is a visualisation of the different structures of tissues below the surface. In the longitudinal axis, it allows the view of a whole fascicle to be captured and analysed for length and pennation angle.

Placement and orientation of the ultrasound probe will affect the picture produced, as it alters the "slice" of the tissue to be examined. Placement refers to the skin-probe interface, and will have little effect on the measurement outcome, provided that the probe is placed along the median longitudinal axis of the muscle (Kawakami et al 2000; Narici et al 1996), with a clearer image being produced using a water-soluble gel over the head of the probe to provide acoustic contact without depressing the dermal surface (Miyatani 2002).

Further validation of US for use in structural assessment is possible and has been attempted using a geometric model to examine fascicle contraction in three-dimensions (examining probe orientation over the muscle) instead of the two-dimensional assumptions (Kawakami et al 2000; Klimstra et al 2007). However, results have been variable; suggesting orientation of the probe on the skin should continue to be standardized at the beginning of an experimental protocol for consistency for all assessors, participants, and interventions, until further validation can be confirmed.

When using US for analysis of subcutaneous fat, it is essential that the measurement protocol is standardized and the investigator is well-trained through repeated measures (the threat to measurement error is minimized by enhancing the measurement reliability of the operator and protocols), as less experienced individuals may compress the skin (causing compression of fat and false low reading; Orphanidou et al 1994) or position the transducer at an angle not perpendicular to the skin (over-measurement/inaccurate reading; Orphanidou et al 1994, Pillen et al 2003).

2.6.2.2.7.1 Validity and reliability of Ultrasound in body composition measures

Ultrasound measurement of varying sites on the body is susceptible to inter-observer variability and has been shown to be affected by practice and/or learning effects during both image capture and analysis phases. Limitations can be broken down into: (1) technique-related (transducer ideally held perpendicular to skin surface, direct compression of subcutaneous fat avoided, Orphanidou et al 1994); (2) anatomy-related; (3) disease-related (severe neuromuscular disorders can lead to unclear muscle outlines, Pillen et al 2003); and (4) patient factors (Rutten et al 2006) such as age (Moukas et al 2002), obesity, and possibly gender (Orphanidou et al 1994) for analysis of diagnostic power. Controlling for these factors prior to measurement is possible, although it can often rely on the experience and sensibilities of the operator and analytical team.

For usable results from US, reliability must apply to both the image reading and acquisition, as the reading is only as good as the quality of the image (Joshua et al 2006). Training and constant practice is essential for accurate repeated measurements. For instance, in echocardiographic imaging of cardiac conditions the American College of Cardiology/American Heart Association recommend “level 2” training as a minimum – 150 studies performed and 300 interpretations under supervision (Seward et al 2002; Kobal et al 2004). Although the World Health Organisation (WHO 1998) suggest that 10% of the time spent training should be devoted to analysis of small parts (as opposed to abdominal, obstetric, and gynaecological examinations) implying that 30-50 practice (training) image-captures would be sufficient to establish a highly reproducible method by an individual (intra-rater reliability).

Table 2.4a summarizes studies reporting the validity of ultrasound against other measures of muscle mass or body composition assessment (in non-CKD). Table 2.4b similarly describes studies reporting the reliability of the ultrasound in repeated measures (in non-CKD).

Table 2.4a - Studies examining validity of Ultrasound, in healthy and unwell groups (ordered by population type and alphabetically by author)

Reference	population type	Tissue/area investigated	ultrasound used (type and frequency)	Participant number N (m,f)	Participant details	Validity compared to…	Mode of assessment (US site/measure)	Correlation co-efficient
ACUTE OR CHRONIC ILLNESS								
Emmons et al 2011 Ultrasound in Med & Biol 37 (5): 734-41	Spinal cord injury (SCI)	abdominal fat	3C- RS 2-5MHz with curvilinear transducer	SCI: 24 males healthy: 20 males	44 ± 10yrs BMI 26.2 ± 5.4 39 ± 11yrs BMI 27.6 ± 4.8	DEXA	Subcut and visceral fat	SCI : "not correlated" Healthy: "correlated"
Thomaes et al 2012 BMC Medical Imaging 12:7	coronary artery disease	quadriceps muscle	B-mode US	20 (Older)	68.3 ± 7.3yrs BMI 26.8 ± 2.8	CT	rectus femoris	0.92 (0.81 - 0.97)
HEALTHY INDIVIDUALS								
Bemben 2002 (abstract only) J Strength Conditioning Research 16(1): 103-8	healthy post-menopausal	upper arm, thigh	5MHz transducer	38f post-menopause 85older (m+f) 10 young mixed (m+f)	58.9 ± 0.7yrs 65.0 ± 0.4yrs 26.1 ± 2.4yrs	MRI	rectus femoris	0.9
Cartwright et al 2013 Muscle & Nerve 47 (4): 515-21	cadavers	skeletal muscle	18-MHz linear-array transducer	4 cadavers		actual measure (by dissection)	bicep brachii/ brachialis complex (mid-arm) tibialis anterior	0.993 0.992
Mendis et al 2010 J Orthop Sports Phys Ther 40 (9): 577-81	healthy	anterior hip muscle	real-time portable US 4 MHz curved linear array transducer	9 (5m, 4f)	24.3 ± 3.5yrs Height: 172.0 ± 11.2cm Weight: 69.6 ± 14.5kg	MRI	iliopsoas sartorius rectus femoris	0.86-0.88 0.81-0.82 0.85-0.89

Table 2.4a (continued) – validity of ultrasound

Reference	population type	Tissue/area investigated	ultrasound used (type and frequency)	Participant number N (m,f)	Participant details	Validity compared to…	Mode of assessment (US site/measure)	Correlation co-efficient
HEALTHY INDIVIDUALS								
Noorkoiv et al 2010a Eur J Appl Physiol 109 (4): 631-9	healthy, young	upper leg	B-mode US (extended field of view) 10MHz linear array probe (60mm width)	6m	28.7 ± 4.6yrs	CT	vastus lateralis ACSA	0.951 -0.998 (p<0.000)
Pineau et al 2007 Ann Nutr Metab 51 (5): 421-7	healthy, middle-aged	body fat	A-mode	41f, 48m	48.4 ± 17.7yrs BMI 28.5 ± 7.7	DEXA	mid-thigh and intra-abdominal	0.98
Volz & Ostrove 1984 (abstract only) Med Sci in Sport and Exercise 16 (1): 97-102	healthy, young	fat thickness	portable ultrasonoscope	66f	18-26yrs	skinfold calipers		0.75-0.86

Presented as mean ± standard deviation unless otherwise stated; IQR = interquartile range; SEM = standard error of the mean; SE = standard error; MTH = muscle thickness; VL = vastus lateralis; ACSA = anatomical cross sectional area; 2-D = 2-dimensional; US = ultrasound or ultrasonography; ns = non-significant result; DEXA = dual energy x-ray absorptiometry; MRI = magnetic resonance imaging; CT = computed tomography; A-mode = amplitude mode; B-mode = brightness mode; BMI = body mass index

Table 2.4b - Studies examining reliability of Ultrasound, in healthy and ill groups (arranged by population type and alphabetically by author)

Reference	population type	Tissue/area investigated	ultrasound used (type and frequency)	Participant number N (m,f)	Participant details	Reliability	US site /measure	Correlation co-efficient
ACUTE AND CHRONIC ILLNESS								
Dudley-Javoroski et al 2010	spinal cord injury (SCI)	vastus lateralis, patellar tendon, soleus, Achilles tendon	B-mode US	16	26 ± 4.5yrs Height: 174 ± 7.1cm Weight: 74.4 ± 13kg	intra-rater reliability		0.58-0.95
Ultrasound Med Biol 36 (10):1594-607			5-12MHz transducer			inter-rater reliability		0.62-0.74
Staehli et al 2010	Osteoarthritis	vastus lateralis	B-mode US	20 post-op	61.5 ± 5.3yrs BMI 27.3 ± 2.3	intra-rater reliability	VL thickness	0.888 (0.778-0.945)
J Electromyography and Kinesiology 20 (6): 1058-65	Total knee arthroplasty (TKA)		10-15MHz	10 pre-op	59.6 ± 6.0yrs BMI 27.5 ± 2.8		VL pennation angle	0.624 (0.345-0.801)
Yang et al 2009	urinary incontinence	pelvic floor		209f	50.8 ± 11.9yrs BMI 24.4 ± 3.9	intra-observer reliability		0.825-0.886
Ultrasound Obstet Gynecol 33(4): 465-71						inter-observer reliability		0.827-0.891
HEALTHY INDIVIDUALS								
Bemben 2002 (abstract only)	healthy post-menopausal	upper arm, thigh	5MHz transducer	38f post-meno 85m+f	58.9 ± 0.7yrs 65.0 ± 0.4yrs	intra-rater reliability	rectus femoris, biceps brachii	0.72-0.99
J Strength Conditioning Research 16(1): 103-8								
Cartwright et al 2013	healthy	skeletal muscle	18-MHz linear-array transducer	4 healthy		intra-rater reliability	bicep brachii/ brachialis complex (mid-arm)	0.984
Muscle & Nerve 47 (4): 515-21							tibialis anterior	0.999
						inter-rater reliability	bicep brachii/ brachialis complex (mid-arm)	0.981
							tibialis anterior	0.998

Table 2.4b (continued) - reliability of ultrasound

Reference	population type	Tissue/area investigated	ultrasound used (type and frequency)	Participant number N (m,f)	Participant details	Reliability	US site /measure	Correlation co-efficient
HEALTHY INDIVIDUALS								
Chumlea & Roche 1986 (abstract only) American Journal of Physical Anthropolgy 71 (3): 351-7	healthy, elderly		A-mode		65-99yrs "elderly"	inter-observer reliability		< 68%
Demura et al 1999	healthy, young	triceps and subscapular	B-mode	16m	21.6 ± 3.6yrs height: 170 ± 5.6cm Weight: 64.8±7.4kg	test-retest reliability	triceps (mm)	r > 0.95
Applied Human Science 18 (2): 43-51				15f	20.4±0.95yrs Height: 160±4.5cm Weight: 55.3±6.0kg		subscapular (mm)	r > 0.92
Hides et al 2007	healthy	abdominal muscles:	B-mode	19 (11f, 8m)	20.3± 5.0yrs Height: 172.0± 9.8cm Weight: 64.5 ±11.4kg	intra-rater (rptd measure of same image)		0.98-0.99
J Orthop Sports Phys Ther 37(8): 480-6		internal obliques and transverse abdominus				intra-rater (of 3 images)		0.62-0.82
						intra-rater (over 2 days)		0.69-0.85
Lin et al 2009	healthy	neck muscles	10MHz linear array tranducer	10 (7f + 3m)	Female: 23.9±2.9yrs BMI 19.5±1.9	intra-session reliability		0.87-0.99
J Orthop Sports Phys Ther 39(12): 850-7					Males: 22.7±1.5yrs BMI 21.5±2.1	inter-session reliability		0.90-0.98
McMeeken et al 2004	healthy	tranverse abdominus	B-mode, 7.5MHz curvilinear transducer	13 (6m+4f)	39.7 SEM 2.3yrs BMI 23.9 SEM 0.8	intra-rater (between days) B-mode	transverse abdominus	0.981
Clin Biomech 19(4): 337-42			M-mode, 5MHz curvilinear transducer			intra-rater (between days) M-mode		0.989
						between instruments (B vs M-mode)		0.817

Table 2.4b (continued) - reliability of ultrasound

Reference	population type	Tissue/area investigated	ultrasound used (type and frequency)	Participant number N (m,f)	Participant details	Reliability	US site /measure	Correlation co-efficient
HEALTHY INDIVIDUALS								
Mota et al 2012 (abstract only) J Orthop Sports Phys Ther 42 (11): 940-6	healthy	abdominal muscle		24f		intra-rater reliability inter-rater reliability	rectus abdominus rectus abdominus	0.74 - 0.90 > 0.90
Muller et al 2013 British Journal of Sports Medicine 47 (16): 1036-43	female athletes (footballers + gymnasts)	adipose tissue (subcutaneous fat)	B-mode	19f	19.5 ± 3.3yrs BMI 21.3 ± 2.3	inter-rater reliability	triceps (mm) subscapular (mm) biceps iliac crest subraspinale abdominal front thigh medial calf overall	0.966 0.917 0.811 0.982 0.96 0.985 0.972 0.953 0.968
Noorkoiv et al 2010a Eur J Appl Physiol 109 (4): 631-9	healthy, young	upper leg	B-mode US (extended field of view) 10MHz linear array probe (60mm width)	6m	28.7 ± 4.6yrs	inter-day reliability	vastus lateralis ACSA	0.982 (0.892-0.997) (p=0.001)
Noorkoiv et al 2010b J Applied Physiol 109 (6): 1974-9	healthy	quadriceps muscle	B-mode US	10m	28 ± 5yrs	inter-rater digitizing reliability intra-session reliability inter-session reliability	vastus lateralis	0.97 (0.88 - 0.99) 0.99 (0.95 - 1.00) 0.95 (0.80 - 0.99)

Table 2.4b (continued) - reliability of ultrasound

Reference	population type	Tissue/area investigated	ultrasound used (type and frequency)	Participant number N (m,f)	Participant details	Reliability	US site /measure	Correlation co-efficient
HEALTHY INDIVIDUALS								
O'Sullivan et al 2007 J Orthop Sports Phys Ther	healthy, asymptomatic	shoulder injury	8MHz linear probe (40mm footprint)	16 (12f, 4m)	20-41 years	intra-rater intra-image (within scan) reliability intra-rater between-scan reliability intra-rater between day reliability inter-rater reliability	thickness measure of lower trapezius	0.99 (0.98-1.0) 0.90-0.99 0.89-0.91 0.88 (0.73-0.96)
Raj et al 2012a Clin Physiol Function Imaging 32(1): 65-70	older healthy	vastus lateralis and gastrocnemius	B-mode real-time 10MHz probe frequency	21 (11m, 10f)	68.1 ± 5.2yrs Height: 164.8 ± 8.9cm Weight: 73.7 ± 10.3kg	intra-rater reliability	muscle thickness pennation angle fascicle length	0.96-0.97 0.85-0.87 0.80-0.90
Thomaes et al 2012 BMC Medical Imaging 12:7	Coronary arterial disease (CAD)	quadriceps muscle	B-mode US 12 MHz linear array transducer	25	68.6 ± 4.6yrs BMI 26.3 ± 3.0	intra-rater reliability		0.97 (0.92 - 0.99)
Volz & Ostrove 1984 (abstract only) Medicine and Science in Sport and Exercise 16 (1): 97-102	healthy, young	fat thickness	portable ultrasonoscope	66f	18-26yrs	test-retest reliability	triceps, biceps, subscapula, suprailiac, abdomen, calf, thigh	0.87-0.99

Table 2.4b (continued) - reliability of ultrasound

Reference	population type	Tissue/area investigated	ultrasound used (type and frequency)	Participant number N (m,f)	Participant details	Reliability	US site /measure	Correlation co-efficient
HEALTHY INDIVIDUALS								
Yoshida et al 2010 (abstract only)	healthy			37m	21.9 ± 2.4yrs Height: 172.9 ± 5.3cm	intra-rater reliability		0.91-0.98
J Sports Rehabilitation 19(2): 149-60					Weight: 66 ± 7.2kg	inter-rater reliability		0.97

Presented as mean ± standard deviation unless otherwise stated; IQR = interquartile range; SEM = standard error of the mean; SE = standard error; MTH = muscle thickness; VL = vastus lateralis; ACSA = anatomical cross sectional area; 2-D = 2-dimensional; US = ultrasound or ultrasonography; ns = non-significant result; DEXA = dual energy x-ray absorptiometry; MRI = magnetic resonance imaging; CT = computed tomography; A-mode = amplitude mode; B-mode = brightness mode; BMI = body mass index

For reasonable precision in reliability, it is suggested that at least 50 participants over three trials are used, measuring the random error ('noise') between trials (within sports medicine and science; Hopkins 2000). Error/variation can be examined by (1) within subject variation, (2) systematic change in mean, (3) retest correlation.

Minimising within subject variation allows smaller changes to be detected in performance or health of a participant. It is the random variation in a measure when an individual is tested many times. The random variability is usually shown as standard deviation (SD), also known as standard error of measurement or typical error in a measurement. Typical error generally increases as the absolute value of measure increases, although the percentage/proportion remains similar (coefficient of variation or CV), allowing direct comparison of measures, irrespective of calibration and/or scaling and can compare the reliability and variation between different modes of measure or equipment.

With correct application of technique, through experience and training and controlling/allowing for other factors (time of day/posture/anatomical sites), ultrasound has been deemed accurate for use in repeated measures (tracking development and detriment). It is also a valid tool compared to a variety of "gold standard" techniques in non-renal populations (Table 2.4b; ICCs consistently >0.80).

2.6.2.2.7.1.1 Limitations of validity and reliability studies of ultrasound to date

Of the studies reporting validity of ultrasound measurements to a gold standard technique (Table 2.4a), only two studies were in in acute or chronic illness, totalling 64 participants (one study compared to DEXA, one to CT). The remaining studies focused instead on able-bodied or healthy participants (six studies, >200 participants, 2 MRI, 1 CT, 1 DEXA, 1 dissection, 1 skinfold calipers) with an age range from 18 to 65yrs. General consensus for these few studies is that US was more well-correlated to the

gold standard in the able-bodied (healthy) individuals than in the acutely or chronically ill participants (r>0.85). However, this cannot conclusively show that utilizing US for assessing body composition in the chronically ill is not possible, as the studies severely lack in number.

Reliability of ultrasound measures (Table 2.4b) were similarly lacking in numbers of studies in the acute or chronically ill populations, with only three studies (summative n=255) examining either inter- or intra-rater reliability. However, correlations ranged from 0.58 to 0.99, suggesting that US is repeatable and reliable, though would require further assessment by new "observers" in new populations. In healthy populations, a greater number of studies (16 studies, 166 participants, age range 18-99years) have shown high repeatability with both intra- and inter-observer correlations exceeding 0.90 for at least one measurement site in each study.

2.6.2.3 Summary for measures of body composition

Table 2.5 summarizes the advantages and disadvantages for each potential measurement technique discussed earlier.

Table 2.5 – Advantages and disadvantages of different body composition measurement techniques

Technique	Advantages	Disadvantages
Dual-energy X-ray Absorptiometry (DEXA/DXA)	• High accuracy and sensitivity • Gold standard for bone mineral density • Quick and painless for the patient	• Exposure to radiation • Expensive to use • Limited access/availability • Very obese may exceed the weight limit of the compartment
Computed (axial) tomography (CT or CAT scan)	• High accuracy and sensitivity • Gold standard for brain scans, organ, and bone assessment • Patient time: 5-10 minutes	• Exposure to radiation • Expensive to use • Limited access/availability
Magnetic Resonance Imaging (MRI)	• High accuracy and sensitivity • Gold standard for imaging any part of the body	• Expensive to use • Limited access/availability • Patients discomfort (claustrophobia) • Patient time: 15-90 minutes
Muscle biopsy	• High sensitivity for assessing small tissue samples • Gold standard for diagnosis of muscle tissue disease • Can assess muscle quality	• Patient discomfort and apprehension • Safety issues/ infection • Requires local anaesthetic • Patient time: 30 minutes plus recovery (10 days before stitches removed)
Body mass index (BMI)= Weight(kg)/ height(m)^2	• Easy to perform/calculate in large population groups • Simple, and standardized • No skill required • Patient time: 1-5 minutes	• Cannot differentiate between muscle and fat • Does not consider fat repositioning with age (peripheral to central)

Table 2.5 (continued) – advantages and disadvantages of body composition measures

Technique	Advantages	Disadvantages
Waist or limb girth (circumference)	• Easy to perform/calculate in large population groups • Simple, and standardized • No skill required • Patient time: 1-5 minutes	• Large potential for error (site specific) • Cannot differentiate between muscle and fat • Does not consider loss of gluteal bulk with ageing
Waist-to-hip ratio	• Easy to perform/calculate in large population groups • Simple, and standardized • No skill required • Patient time: 1-5 minutes	• Cannot differentiate between muscle and fat
Skinfold thickness (calipers)	• Inexpensive after initial outlay for equipment • Simple and quick	• Extensive training required by operator • Large potential for error (site specific) • Less accurate in very lean/ thin participants, and obese, than participants in the “mid-range”
Underwater/ hydrostatic weighing	• High accuracy and sensitivity • Gold standard for measuring body volume	• Cost and labour intensive • Patient discomfort and apprehension • Safety issues • Limited access/availability
Urine analysis (creatinine or 3-methyl-histidine)	• Highly sensitive • Used as a proxy to measure muscle breakdown • 3-MH in urine is proportional to total muscle mass	• Requires 24-hour collection of urine by patient • Inconvenient for participant • Creatinine assessment imposes a limited diet in previous 24-hours (meat-free)

Table 2.5 (continued) – advantages and disadvantages of body composition measures

Technique	Advantages	Disadvantages
Total body potassium (TBK)	• Highly sensitive • Measures radiation (^{40}K) as a proxy for FFM	• Expensive • Limited access/availability • Imposes restriction on participants (no radiographic medical procedures in previous week)
Bio-electrical Impedance Analysis/ Spectroscopy (BIA/ BIS)	• High accuracy and sensitivity • Portable • Inexpensive after initial outlay for equipment • Can differentiate between fat and muscle • Patient time: 10-20 minutes	• Hydration condition must be maintained by participant • Cannot observe muscle quality
Ultrasound (US)	• Moderate accuracy and sensitivity • Reliable /repeatable • Inexpensive after initial outlay for equipment • Portable • Can differentiate between tissues	• Requires extensive training by operator • Patient time: 20-45 minutes

Studies investigating the wasting and rehabilitation of the quadriceps found insignificant differences between gold standard techniques and US, concluding that the level of precision is high enough to use ultrasound for this type of research (Tables 2.4a-b). There are limitations and risks associated with the use of US (such as the accuracy of individual results); however, considering the "gold standard" expense and availability for use at varying anatomical sites and tissue type, alongside radiation exposure, anaesthesia (increased risk to children; Pillen et al 2003) and time

constraints, the relative ease and accessibility of US has become a standard and well-accepted alternative in clinical and field settings to assess body composition.

2.7 Anabolic interventions to affect body composition in Chronic Kidney Disease

Loss of skeletal muscle mass is due to reduced protein synthesis, increased degradation, or an imbalance between the two (Fearon et al 2012; Balstad et al 2014). Anabolic therapy stimulates metabolic pathways to increase muscle mass. Potential anabolic effects on muscle mass should be targeted in cachexia (general wasting) prevention and treatment, but anti-catabolic effects (to decrease the breakdown of protein) are also of vital importance. The need for additional protein to overcome the negative balance and malnutrition cannot be solved by simply increasing protein intake in food, as this in turn can aggravate uraemia (Workeneh & Mitch 2010). Therefore anabolic interventions to increase protein production and reduce loss are vital.

Table 2.6 shows studies to date that have assessed body composition in Chronic Kidney Disease across several stages of the disease trajectory. Many of these studies were cross-sectional or longitudinal, whereas others have intervened with some form of anabolic therapy. Measurement techniques employed include BIA, anthropometry (limb and trunk girth/circumference), skinfold thickness, DEXA, CT, near-infrared, ultrasound, and standard BMI.

Table 2.6 - Studies examining body composition in CKD (non-dialysis and dialysis) patients (ordered by CKD stage, study design, and alphabetically by author)

Author, year, journal	CKD stage	study design	participant number n (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
PRE (NON) DIALYSIS STUDIES											
PRE (NON) DIALYSIS STUDIES - CROSS-SECTIONAL AND COMPARATIVE STUDIES											
Avesani et al 2001	pre-dialysis diabetic	comparative diabetic CRF vs non-diabetic	diabetic CRF: 24 (18m, 6f) 57±10.6yrs	none		lean body mass kg diabetic		52 ± 9.1			
Nephrology Dialysis Trnsplantation 16: 556-60			non-diabetic CRF: 24 (18m, 6f) 55.4±11.3yrs			lean body mass kg non-diabetic		51 ± 8.3			ns
						body fat % diabetic		24.7 ± 10.6			
						body fat % non-diabetic		24.6 ± 8.61			ns
Bellizzi et al 2006	CKD3-5	comparative	CKD: 84 (49m, 35f)	none		BIA fat free mass kg male		57.3 ± 9.2		<0.05 gender difference	<0.05
Journal of the American Society of Nephrology 17: 1481-7	CKD3 (n=32)		CKD3 (n=32) 65.8±10.9yrs BMI 26.6±4.4			BIA fat free mass kg female		41.9 ± 6.9			
	CKD4 (n=31)		CKD4 (n=31) 62.9±11.6yrs BMI 26.1±4.2			BIA body cell mass kg male		26.0 ± 4.3		<0.05 gender difference	<0.01
	CKD5 (n=21)		CKD5 (n=21) 60.1±16.2yrs BMI 25.5±5.3			BIA body cell mass kg female		15.3 ± 2.5			<0.01
			healthy control matched: 604 (298M,306F)			BIA fat mass % male		20.3 ± 7.1		<0.05 gender difference	<0.01
						BIA fat mass % female		30.4 ± 7.3			

Table 2.6 (continued) – body composition in CKD

Author, year, journal	CKD stage	study design	participant number n (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
PRE (NON) DIALYSIS STUDIES - CROSS-SECTIONAL AND COMPARATIVE STUDIES											
Carvalho et al 2012	CKD 3-4	cross sectional and longitudinal	44 (66%M)	none	12 months	total body fat % male	25.9 ± 7.7	26.4 ± 7.4		ns	
Nephrology Dialysis Transplantation 27: 1423-8	CKD3 (n=25) CKD4 (n=19)		62.9±13.9yrs BMI 25.5±5.1			total body fat % female	38.1 ± 6.8	38.4 ± 7.0		ns	
						waist circumference cm male	89.5 ± 11.1	90.1 ± 12.1		ns	
						waist circumference cm female	88.6 ± 12.7	89.2 ± 9.4		ns	
						mid-arm muscle circumference (% of healthy matched)	85.9 ± 11.4	89.7 ± 13.9		0.01	

Table 2.6 (continued) – body composition in CKD

Author, year, journal	CKD stage	study design	participant number n (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
PRE (NON) DIALYSIS STUDIES - COHORT STUDIES (PROSPECTIVE, RETROSPECTIVE ETC)											
Castaneda-Sceppa et al 2007	CKD 3-4	Longitudinal (prospective cohort)	780 (62%M)	none	12 months	arm muscle area cm2 male	46 ± 12	45 ± 11	-1.0 ± 5.8	ns	
Journal of Renal Nutrition 17 (5): 314-22			52±12yrs			arm muscle area cm2 female	29 ± 12	29 ± 13	0.1 ± 7.8	ns	
Chang et al 2011	non-dialysis	prospective cohort (observational)	128 (60M, 68F)	none	for pre-dialysis period	mid-arm circumference (cm)	28.0 ± 3.6				
Nephrology Dialysis Tranplantation 26: 3588-95	CKD1 (n=9)		Total: 60.7±14.8yrs Height 159.2±7.3cm Weight 62.9±10.7kg		~33.8 ± 9.2 months	triceps skinfold thickness mm	21.7 ± 9.2				
	CKD2 (n=35)					mid-arm muscle circumference cm	21.3 ± 3.4				
	CKD3a (n=18)					mid-arm muscle area cm2	36.9 ± 11.4				
	CKD3b (n=17)					total body fat %	27.1 ± 9.9				
	CKD4 (n=31)					BIA total body fat kg	17.4 ± 7.2				
	CKD5 non-dialysis (n=18)					BIA lean body mass kg	45.2 ± 9.2				

Table 2.6 (continued) – body composition in CKD

Author, year, journal	CKD stage	study design	participant number n (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
MIXED STAGE STUDIES											
MIXED STAGE STUDIES - CROSS-SECTIONAL AND COMPARATIVE STUDIES											
Khan et al 2009	all stages	cross sectional	40 (23m, 17f)	none		triceps skinfold thickness mm	13.3 ± 4.12				
Journal of Renal Nutrition 19 (4): 275-82			55±12.2yrs Height 161±6cm Weight 61.6±11.7kg			biceps skinfold thickness mm	10.07 ± 3.5				
			BMI 24.2±4.3			mid-arm circumference cm	23.1 ± 3.15				
						mid-arm muscle circumference cm	19.6 ± 2.1				
						waist-to-height ratio	0.92 ± 0.08				
Nielsen et al 1994	predialysis	comparative	pre-d: 30 (20m, 10f)	none		DEXA lean body mass kg pre-d		47.8			<0.05 to control
Advances in Peritoneal Dialysis 10: 99-103	"severe" CKD4 GFR <30ml/min	pre-dialysis, PD, normal/ healthy	PD: 20 (11m, 9f)			DEXA lean body mass kg PD		47.2			<0.05 to control
	and dialysis (PD)		control: 62 (12m, 50f)			DEXA lean body mass kg control		43.6			
MIXED STAGE STUDIES - COHORT STUDIES (PROSPECTIVE, RETROSPECTIVE, ETC)											
Dumler & Kilates 1999	pre-dialysis, HD, and transplant	prospective cohort	pre-dialysis: 35 (54%M, 46%F) 61±12yrs	none	9 months	HD BIA body cell mass		24 ± 7			
Mineral and Electrolyte Metabolism 25: 397-9			Weight 91±24kg BMI 30.9±6.6			HD BIA fat free mass		54 ± 14			
			HD: 58 (57%M,43%F) 71±16yrs BMI 24.5±4.9			pre-d BIA body cell mass		28 ± 8			<0.01 to HD and transplant
						pre-d BIA fat free mass		62 ± 17			<0.01 to HD and transplant

Table 2.6 (continued) – body composition in CKD

Author, year, journal	CKD stage	study design	participant number n (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
DIALYSIS - HD											
DIALYSIS - HD - CROSS-SECTIONAL AND COMPARATIVE STUDIES											
Bross et al 2010	HD	cross sectional observational	118 (68m, 50f) 49.4±11.5yrs	none		DEXA body fat %		28.9 ± 10.1			
American Journal of Kidney Diseases 55 (5):		validation	BMI 27±6			Near infrared (NIR) body fat %		26.4 ± 10.4			
885-96						tricep skinfold for body fat %		31.0 ± 8.4			
Huang et al 2010	HD	Comparison study	1709	high or low dialysis dose		triceps skinfold thickness mm	16.3 ± 7.9				
Kidney International 77 (7): 624-9			Age mean 58yrs BMI mean 25.2			mid-arm muscle circumference cm	24.8 ± 3.8				
Ishihara et al 2010	HD	cross sectional comparison	80 (54m, 26f)	none	30 years	triceps skinfold thickness mm	8.1 ± 4.6				
Blood Purification 33(3): 161-5		by dialysis duration	65.4±12.3yrs Height 161.4±10cm Weight 54.9±13.3kg BMI 20.9±3.6			mid-upper arm muscle area cm2	39.4 ± 10.3				
						TSF mm <10yrs	9.2 ± 5.3				
						TSF mm >30yrs	6.5 ± 4.2				<0.05
						MAMA cm2 <10yrs	1.01 ± 0.22				
						MAMA cm2 >30yrs	0.79 ± 0.13				<0.001
Kaizu et al 1998	HD	comparison	45 (21m, 24f)	one dialysis session		body weight kg high IL6			-1.9 ± 0.7 (-4%)		<0.05
American Journal of Kidney Diseases 31 (1):		low inflammation	59.1±1.9yrs (range 23-80yrs)			body weight kg low IL6			↑		
93-100		vs high inflammation				MAMA cm2 high IL6			↓		
						MAMA cm2 low IL6					<0.05

Table 2.6 (continued) – body composition in CKD

Author, year, journal	CKD stage	study design	participant number N (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
DIALYSIS - HD - CROSS-SECTIONAL AND COMPARATIVE STUDIES											
Kato et al 2011	HD	cross sectional	161 (113m, 48f)	none		Abdominal visceral fat area cm2	83.3 ± 68.2				
Nephrology dialysis Transplantation 26: 1967-76			61±11yrs BMI 20.7±2.8			abdominal subcutaneous fat area cm2	127.8 ± 63.6				
						thigh muscle area cm2	180.8 ± 57.4				
MacDonald et al 2004	HD	comparative	ESRD 17 (12M,5F) 58±3.4yrs Height 167.4±1.9cm BMI 26.6±1.1	none		DEXA total fat mass kg	25.1 ± 2.9				ns
Journal of Renal Nutrition 14 (4): 248-52		cross-sectional	healthy 17 (12M,5F) 55.5±2.7yrs Height 170.8±2.4cm BMI 26.4±0.6			DEXA bone mineral content kg	2.3 ± 0.1				<0.05
						DEXA appendicular lean mass kg	17.6 ± 0.9				<0.05
DIALYSIS - HD - COHORT STUDIES (PROSPECTIVE, RETROSPECTIVE, AND LONGITUDINAL)											
Kalantar-Zadeh et al 2012	HD	retrospective cohort	121,762 (45%F) 62±15yrs	usual dialysis care	up to 5 years	dry weight kg	75.4 ± 21.1				
American Journal of Epidemiology 175 (8): 793-803		regression analysis	Dry weight 75.4±21.1kg Height 168±11cm BMI 26.8±7.0		~738 days						

Table 2.6 (continued) – body composition in CKD

Author, year, journal	CKD stage	study design	participant number n (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
DIALYSIS - HD - COHORT STUDIES (PROSPECTIVE, RETROSPECTIVE, AND LONGITUDINAL)											
de Oliveira et al 2012 Journal of Renal Nutrition 22 (3): 307-16	HD	follow up (prospective cohort)	143 (83m, 60f) 52.2±16.6yrs (range 20-83yrs) BMI mean 23.0	usual dialysis care	12 months	triceps skinfold thickness mm male	10.25 ± 4.72				<0.001 gender difference
						triceps skinfold thickness mm female	14.88 ± 6.39				
						mid-arm circumference (cm) male	28.00 ± 4.18				ns
						mid-arm circumference cm female	26.88 ± 4.30				
						mid-arm muscle circumference cm male	24.78 ± 3.30				<0.001 gender difference
						mid-arm muscle circumference cm female	22.23 ± 2.95				
						mid-arm muscle area cm2 male	49.74 ± 13.11				<0.001 gender difference
						mid-arm muscle area cm2 female	40.02 ± 10.97				
						Adductor pollicis muscle thickness mm male	12.34 ± 1.55				<0.001 gender difference
						adductor pollicis muscle thickness mm female	11.19 ± 1.51				

Table 2.6 (continued) – body composition in CKD

Author, year, journal	CKD stage	study design	participant number n (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
DIALYSIS - HD - COHORT STUDIES (PROSPECTIVE, RETROSPECTIVE, AND LONGITUDINAL)											
Takahashi et al 2003	HD	prospective longitudinal	46 (28m, 18f)	usual dialysis care	4 years	DEXA lean body mass kg	38.6 ± 7.8	37.1 ± 7.7		<0.01	
Clinical Nephrology 59 (5): 373-8			52±11.4yrs BMI 21±2.4			DEXA fat kg	11.5 ± 5.6	12.3 ± 6.0		<0.05	
						DEXA fat %	22.1 ± 10.3	23.8 ± 10.0		<0.05	
DIALYSIS - HD - RANDOMISED CONTROLLED TRIALS											
Hansen et al 2000	HD	RCT	GH: 9 (5m, 4f) 44.4yrs (range 18.4-63.9yrs)	injections: growth hormone (GH)	6 months	DEXA total fat mass kg	11.5 SEM 2.14	8.45 SEM 1.58	3.05 SEM 0.75	<0.001	0.005
Clinical Nephrology 53 (2): 99-107			pla: 11 (7m, 4f) 48.3yrs (range 18.8-68.5yrs)		daily	DEXA lean tissue mass kg	43.6 SEM 3.83	46.75 SEM 3.93	3.14 SEM 0.42	<0.001	0.0001
Mortelmans et al 1999	HD	RCT	16 (9m, 7f)	parenteral nutrition	9 months during dialysis (3/ week)	body weight kg	54.8 ± 10.1	57.1 ± 10.7	> 2.0	<0.05	
Journal of Parenteral and Enteral Nutrition 23 (2): 90-5			66±10yrs Weight 54.8±10kg BMI 20±3			triceps skinfold thickness mm	8.1 ± 4.2	9.7 ± 48		<0.05	
						arm muscle circumference cm	21.6 ± 3.4	22.3 ± 3.3		0.07 (ns)	
DIALYSIS - PD											
Soreide et al 1992	PD	longitudinal	8m	usual dialysis care	6-8 months	Near infrared (NIR) body fat %	19.8 ± 2.9	22.5 ± 3.0		<0.05	
Advances in Peritoneal Dialysis 8: 173-6 (abstract)											

Table 2.6 (continued) – body composition in CKD

Author, year, journal	CKD stage	study design	participant number n (m,f) and further details	intervention	time/ duration	Mode of assessment and outcome measures	pre intervention (baseline values)	post intervention (final values)	actual / percentage change reported	significance (p)	group difference (p)
DIALYSIS - HD AND PD											
DIALYSIS - HD AND PD - CROSS-SECTIONAL OR COMPARATIVE STUDIES											
Saxenhofer et al 1992	ESRD	comparative	HD: 11m	none		CT muscle mass				ns	
Clinical Nephrology 38 (4): 219-23 (abstract)	(HD vs PD)	HD vs PD	PD: 11m			CT body fat distribution				ns	
DIALYSIS - HD AND PD - COHORT STUDIES (PROSEPCTIVE, RETROSPECTIVE, ETC)											
Antunes et al 2010	HD and PD	prospective	79 (48m,31F) 60 IQR 50-71 yrs	usual dialysis care		survivors BIA body fat %		29.2 IQR (21.7, 36.8)			
Renal Failure 32 (9): 1055-9		survivors vs non-survivors	BMI 24.1 IQR 21.5-27.2			non survivors BIA body fat %		38.2 IQR (28, 42.6)			0.017
Pupim et al 2005	ESRD	prospective	142 (91M,51F) 52.8±1yrs	usual dialysis care	12 months	body weight kg				ns	
Kidney International 68: 2368-74			Weight 74.2±1.2kg BMI 24.9±0.4			lean body mass kg			-1.6		
						fat mass kg			1.6		
DIALYSIS - HD AND PD - RANDOMISED CONTROLLED TRIALS											
MacDonald et al 2007	CKD 5 (HD or PD)	RCT	34 (29M,5F) ~55yrs	nandrolone deconate	24 weeks	DEXA appendicular lean mass kg high dose	19.9 SEM 1.1	21.9 SEM 1.2	3.148	0.008	<0.05 to control and low dose
Nephron Clinical Practice 106: 125-35				low/mediu m/ high dose	once/wk	DEXA total lean mass kg high dose	50.4 SEM 2.3	55.4 SEM 3.0	3.388	0.001	<0.05 to all groups
Johansen et al 1999	HD (20) and PD (9)	RCT	29 (23m, 6f) 47±13yrs BMI 25.8±6.6	nandrolone deconate or placebo	6 months	body weight kg			1.8 ± 2.3	0.03	ns
Journal of the American Medical Association 281: 1275-81			drug: 14 placebo: 15		once/ week	lean body mass kg			4.5 ± 2.3	<0.001	0.005
						body fat kg			-2.4 ± 2.9	0.02	

Presented as mean ± standard deviation unless otherwise stated; IQR = interquartile range; SEM = standard error of the mean; SE = standard error; RCT = randomised controlled trial; nonRCT = non randomised controlled trial; Xover = crossover design; exp = experimental group; co/con = control group; pla = placebo group; MTH = muscle thickness; VL = vastus lateralis; CSA = cross sectional area; PRT = progressive resistance training; 2-D = 2-dimensional; US = ultrasound or ultrasonography; ns = non-significant result; HD = haemodialysis treatment; PD = peritoneal dialysis treatment; ESRD = end-stage renal disease; CT = computed tomography; DEXA = dual energy x-ray absorptiometry; MAMA = mid-arm muscle area; TSF = total skinfold; BIA = bioelectrical impedance analysis; CKD1…5 = stage of disease (1-5)

2.7.1 Nutritional Interventions

Starvation or amino acid insufficiency leads to decreased protein synthesis and possibly increased protein degradation. However, inadequate dietary intake is not likely to be the principal cause of muscle atrophy as many CKD patients do not have a net negative muscle protein balance compared to healthy controls (Lim & Kopple 2000, Ikizler 2009). Studies investigating nutritional supplementation have not directly measured muscle protein balance, but have demonstrated an increase in serum albumin concentration, possibly due to increased liver protein synthesis, or the effect of reducing inflammation (Cano et al 2007; Friedman & Fadem 2010).

For CKD patients undergoing regular peritoneal dialysis, an amino acid dialysate (or amino acid and glucose dialysate when compared to glucose alone) has previously brought about an anabolic effect (Kopple et al 1995; Delarue et al 1999; Tjiong et al 2005). Though clearly this needs further investigation in peritoneal dialysis and for use in haemodialysis patients, and is not viable for dialysis-independent patients (non-dialysis).

Total parenteral nutrition or TPN (HD only; Mortelmans 1999; Table 2.6) involves feeding a person intravenously, bypassing the usual process of eating and digestion. Positive effects can be the easy addition of calories into the body, but as the authors of this study noted in the discussion, much of the intake may have been transformed into fat (not protein or muscle).

2.7.2 Anabolic Hormone therapy

Administration of exogenous growth hormone (Hansen 2000; Table 2.6) has an anabolic effect through the increase of protein synthesis with no change in the rate of degradation; although patients with inflammation (high levels of c-reactive protein) may not respond. Nandrolone Deconoate (in dialysis reviewed by Johansen 1999; MacDonald 2007; Table 2.6) is an anabolic steroid known to elicit

"positive effects" including muscle growth, appetite stimulation, and increased red blood cell production and bone density. Clinical studies have also shown anabolic steroids to be effective in treating anaemia (aplastic anaemia, van Hengstum et al 1979; fanconi anaemia, Rose et al 2014). Potential negative effects of the intervention can vary (Hinterberger & Vierhapper 1993; Kuipers 1998), but include possible damage to the cardiovascular system if taken in very high doses (Sullivan et al 1999), which may exclude some of the CKD population from their use. Though supplementation has shown positive results in muscle mass in intervention trials (alone or in combination with resistance training; Johansen et al 2006; Johansen et al 1999), additional information is needed before testosterone replacement therapy can be widely recommended due to its side-effects, especially in women (Workeneh & Mitch 2010).

2.7.3 Limitations of these anabolic (non-exercise) intervention studies

Out of a total of 25 studies: 17 took place in patients already undergoing regular dialysis (eleven in HD, one in PD, five in mixed dialysis forms), three studies used all stages (dialysis and pre-dialysis), with only five studies purely examining pre-dialysis patients, despite them making up the majority of the CKD population. Of the 25 studies, only four were RCTs. The largest study found (>100,000 participants) was a retrospective cohort study examining the effect of usual dialysis care over a five year period (Kalantar-Zadeh et al 2012).

Total participant number in other treatment groups and at different stages were reported as 245 (mixed stage studies) and 1084 (non-dialysis dependent studies). The male/female split was largely representative of the general CKD population (Chronic Renal Failure: approximately twice as many males up to age 75 years, then three-times as many males than females over 75 years, Jungers et al 1996; the overall risks of all-cause mortality and cardiovascular mortality are higher in men at all levels of kidney function, Nitsch et al 2013) for those that reported it. However

there were no anabolic interventions where body composition was assessed as a primary outcomes measure in non-dialysis and mixed stage studies (all comparative, cross-sectional, or longitudinal observation/cohort studies).

In the dialysis dependent studies the focus has been primarily HD, though this is expected as a larger proportion of dialysis patients undergo HD than PD (<2% of dialysis patients use PD in the UK and most countries worldwide; Oxford Handbook of Dialysis 2004). The 17 studies here in dialysis patients (11 HD, 1 PD, 5 HD or PD) totaled over one-hundred thousand patients, of which fewer than 100 were included in RCTs (n=99). As with earlier-stage studies, males made up a larger proportion of the sample and were thus representative of the standard CKD population in ESRD.

2.7.4 Exercise training

With regards to the mechanisms of muscle protein turnover, few studies have investigated the effect of exercise training on CKD patients specifically. One study - Kopple et al (2007) - examined HD patients assigned to different exercise groups (strength, endurance, half-strength plus half-endurance) or a control, trained approximately 21-weeks, and examined changes in markers of protein synthesis and degradation. All three exercising groups showed similar changes in these factors, contrary to the expectation of greater changes in the resistance/strength training group. Conversely, endurance exercise appeared to suppress the rate of protein degradation more than the strength training. However the extent of the suppression was not of the same magnitude as the increased synthesis in all exercising groups. Actual muscle size or structure were not measured in the study, nor was muscle strength or endurance capacity, so how these chemical markers translate to potential benefits is unclear. Thus further study into the response to exercise is required in both dialysis and non-dialysis CKD patients.

It had previously been assumed that due to the extensive wasting observed in CKD patients, any exercise stimulus would bring about an anabolic (or anti-catabolic effect). However investigation comparing a control group with three different training interventions in CKD5 HD patients (RT only, endurance/aerobic only, mixed RT plus endurance/aerobic training; Kopple et al 2007) reported increased muscle IgF-1 mRNA (insulin-like growth factor 1; plays an important role in growth and has anabolic effects. mRNA; codes for the chemical blueprint of protein during protein synthesis) in response to exercise but no increase in muscle size, which was surprising. Another study (Wang et al 2009) examined this phenomenon in animal models (using mice), once again comparing RT (muscle overload) and endurance (treadmill running) exercise. Findings indicated that whilst endurance exercise did bring about reduced catabolism (muscle proteolysis), it did not improve (increase) protein synthesis whereas RT group improved both measures (reduced catabolism and increased anabolism), thereby highlighting the benefit of resistance/strength training over endurance/aerobic exercise in a population vulnerable to muscle wasting.

2.7.4.1 Resistance/Strength training

Essential for the maintenance and restoration of lean mass, resistance exercise increases the rate of anabolism, and leads to a greater proportion of weight gain as lean tissue, not fat mass. Defined as muscle movement against a resistance, it is a potent anabolic stimulus, promoting muscle growth and strengthening in asymptomatic, healthy individuals (Frontera et al 1988).

Resistance training is often implemented in rehabilitation programmes (easy and low risk) and studies regularly show an improvement in strength; positively affecting other outcome measures, including the ability to perform simple and more complex ADLs (Casaburi 2005). Promotion of resistance training alone has often been discouraged and avoided as many hypotheses suggest that strength training using high load would compromise the capillarisation and oxidative potential of the

muscle fibres. Green et al (1999) tested this hypothesis, showing that 12-weeks of high resistance training (regime typical of exercise testing studies) did not negatively affect either, even in the presence of muscle fibre hypertrophy.

Strength gains through (progressive) resistance training would effectively reduce the patients' perception of muscular fatigue during and following a training session (or performance of any activity) which is often a major limiting factor in rehabilitation programmes (Hamilton et al 1995). As increased fatigability during exercise can partially be attributed to a reduced oxidative capacity of the skeletal muscle (Maltais et al 1996) also improved through a programme of strength training in older (healthy) subjects (Frontera 1990).

Increases/improvements in muscular strength and power through PRT has not always been associated with subsequent benefits in function (functional performance) as other factors (unaffected by strength training) may still influence the level of disability experienced (Ouellette et al 2004). There is conflicting evidence in this area, particularly when examining the effects of resistance training alone (without aerobic intervention; Weiss et al 2000) as the training can lack specificity and application to functional tests which assesses muscular endurance and velocity (timed stair climb, timed up and go, 6-min walk test). The conflicting data often arises as exercise duration, intensity, frequency, and sets/reps, alongside use of varying outcome measures leads to a lack of comparability.

Strength gains in healthy subjects are generally brought about through an amalgamation of muscular hypertrophy and improved neural recruitment. Neural improvement is suggested when there is a proportionally greater strength gain than there is increase in cross-sectional area (hypertrophy). Structural adaptation is attributable for increased strength when utilising equipment with unfamiliar movement patterns (i.e. apparatus which the subjects have not trained on). Muscle fibre hypertrophy has been shown to have a delayed response to training, only

being observed after several weeks (7 weeks; Green et al 1999), with the specificity of the training programme dictating whether a differential increase in area is observed between fibre types.

A further delay has been experienced in capillarisation (increased number of capillary-fibre contact points), as many shorter programmes do not report this adaptation with training (Hather et al 1991, McCall et al 1996, noticeable at 12weeks; Green et al 1999). Programme specificity and focus on movement type has been suggested to also influence the capillary-to-fibre (C-F) area ratio, as concentric contraction alone appears to have no effect on C-F ratio, compared to interventions utilising both concentric and eccentric movement such as free-weight training.

Observations during and following combination exercise showed that resistive training induced proportionally less dyspnea (shortness of breath) than an aerobic component and was therefore tolerated well by COPD patients (Bernard et al 1999, Simpson et al 1992). Although high intensity strength training could be problematic for those already suffering from the effects of bone-wasting or injury (including fractures), the effects on bone density in those with potential to develop osteoporosis could be beneficial, helping to postpone onset of the disease (Bernard et al 1999, Heinonen et al 1996). Minimising muscular atrophy has been shown to aid the attenuation of bone mineral loss, demonstrating a strong correlation between normalisation of muscle mass and normalisation of bone mass (Bloomfield et al 1997, Zeman et al 1991).

In an otherwise healthy population, neuromuscular decrements (decreased motor-neuron excitability) from 5weeks enforced immobilisation were shown to be fully reversible with 18weeks of strength training (Sale et al 1982; Bloomfield et al 1997).

In both the healthy and ill, trained and untrained population, studies have shown varying results in strength, size, power, and endurance measures following a range of interventions. Current ACSM guidelines would recommend low repetitions, high resistance (for optimal gains in strength) and high reps, low weight (for endurance), performed 3-4 times per week, increasing sessions as experience grows. This is a contentious issue as many studies have shown contradictory findings, especially with regard to the number of sets (of repetitions) and training sessions to be performed each week (Smith & Bruce-Low 2004), suggesting that training a muscle group in a single set (to muscular failure), no more than twice per week (and often just once) showed no difference in outcome measures than training at 3, 4, or 5 sets in each session.

Ideas have been put forward that isolating an area to be trained (e.g. only lower body) will lead to greater gains (localised strength and muscle mass) than whole-body training (same intervention for lower body, plus upper work). However, it has shown to have no significant effect between the two groups (Campbell et al 2002) as the number of muscle groups involved in training did not affect the extent of muscle hypertrophy (even in the absence of adequate protein intake).

2.7.4.2 Endurance/ Aerobic exercise

Aerobic activity training as part of patient rehabilitation has been strongly associated with improved exercise endurance and tolerance (Bernard et al 1999), quadriceps fatigability, and HRQoL (Mador et al 2004; Casaburi et al 2005) but with little effect on muscle atrophy and weakness (no strength gains). Force maintenance (muscular endurance) can take longer to return following a period of immobilisation/inactivity in an otherwise healthy population, and is often found to still be lower than previous levels even after muscular strength (weight bearing exercises) has fully recovered (Tesch et al 1991; Bloomfield 1997).

Influencing factors of muscle strength and mass may require less time for recovery than those contributing to muscular endurance as disuse causes loss of efficiency in O_2 delivery and utilisation (fall in oxidative enzyme activity in vastus lateralis and soleus; Hikida et al 1989). It is thus vital that any intervention program design is aware of an increased risk of bone fracture and injury (even with normalisation/recovery of muscular strength) in osteopaenic-prone groups (Bloomfield 1997).

Continuous exercise training (20mins at ≥70% max exercise capacity) has been shown to be effective (clinically important improvements in HRQoL) when the protocol is achieved fully (Puhan et al 2006). However survivors and patients of critical and chronic illnesses are often unable to tolerate continuous exercise in this way, leading to lower levels of success and long term adherence to the prescribed intervention. Interval training has had reportedly lower levels of dyspnea (shortness of breath), and generally greater adherence/compliance, although the level of effectiveness (in comparison) has been debated. Evidence implies that little difference exists between the outcomes measured after 15 sessions (over 3weeks; Puhan et al 2006), with significantly greater adherence for protocol completion and throughput (Coppoolse et al 1999; Vogiatzis et al 2002; Sabapathy et al 2004 – all in COPD patients) and increased short-term maximal capacity above that seen in continual intensity training interventions. This shows a practical and successful method of initiating exercise in patients unable to tolerate large amounts of higher intensity exercise. A greater volume of work is accumulated with continuous exercise, and benefits of this could be useful to the patient and researcher later in the development of strength and tolerance.

Supported upper extremity endurance exercise was implemented alongside general physiotherapy to investigate the impact and practicality of the intervention in critically ill patients (instead of just the usual lower-extremity exercise routinely performed). Training early on in recovery (within 96 hours of weaning from

mechanical ventilation) later improved exercise tolerance (more so in those with higher baseline inspiratory muscle strength) significantly (Porta et al 2005). The effect of this physiotherapy was unaffected by patient age, BMI, or length of stay in an intensive care unit (ICU). Aerobic training for 7-weeks has been shown to improve exercise tolerance and aerobic capacity (Burini et al 2006), but functional gain relies on a specific task being performed/trained, highlighting that endurance exercises may train cardiopulmonary responses to set workloads, though it may not modify the course of illness or its clinical expression significantly.

2.7.4.3 Combination exercise programmes

Programmes/interventions of this nature are often varied in their ratio (aerobic/resistance). Theoretically, a combined protocol should offer the joint benefits of each component. However, mixed approaches are often limited by time, and thus a full programme of each is not offered, but a pooling of their truncated versions.

The question must therefore arise as to whether this is appropriate and effective. Examining patients with COPD in rehabilitative studies (Bernard et al 1999) has shown that the additional strength training alongside current aerobic practice can be well-tolerated despite the severity of the disease, with the combination of aerobic and resistance exercises bringing about greater improvement in muscular strength and endurance, and muscular hypertrophy, than with aerobic alone.

2.7.5 Exercise Intervention Research in CKD

A review of anabolic interventions in end-stage renal disease (CKD5, Storer 2009) examined exercise interventions (endurance, combination, resistance programmes) and androgen and growth hormone therapies to determine what improvements could made in physical function. Progressive resistance training offers the greatest potential for producing an anabolic effect (Galvao et al 2005) but due to the significant atrophy, chronic catabolism, and uraemic myopathy in these patients a

large “adaptation window” is open providing the often weak stimuli implemented in endurance programmes to bring about skeletal muscle anabolism (Storer 2009). In contrast to PRT in healthy individuals, Storer noted no significant increases in lean body mass or reduction in fat mass, although the trained quadriceps muscle cross-sectional area did increase (Johansen et al 2006).

Resistance training has been utilised as an adjunct therapy to muscle atrophy in CKD, using light handheld weights to develop strength and functional capabilities more specific for activities of daily life (ADLs). A review by Kouidi (2002) recommended resistance training following the main aerobic/interval part of a training session, or on a separate day. Some studies have successfully shown advantages of PRT *prior* to aerobic exercises (Oh-Park et al 2002; Ridley et al 1999) with greater compliance, as often patients would complain of fatigue post-aerobic component, unable to complete the resistance exercises, if PRT *followed* aerobic. Increasing muscular endurance (low weight, high repetitions) and strength (high weight, low repetitions) should be progressed by increasing sets as the desired workload is attained.

A study of resistance training to mitigate (lessen) the effects of a low-protein diet, demonstrated that training at 80% 1RM, 3 times/week, led to an increase in GFR from 24.8 to 26.4mL/min in 12 weeks, compared to the control group whose GFR fell in the same period (30.0mL/min to 28.0mL/min, group difference $p<0.05$; Castaneda et al 2001). As dialysis is generally initiated at a GFR value of 15ml/min or less, this indicates a positive clinical effect of resistance training that overcomes the necessary implementation of a low-protein diet. This clinical improvement occurred alongside strength gains of approximately one-third (knee extension ↑47 ± 24%, leg press ↑ 29 ± 15%) compared to a control decline or no significant change ($p<0.001$; Castaneda et al 2001). These participants were pre-dialysis (CKD3b-4) patients, where increasing the GFR is an additional step away from dialysis, and nearer to health.

Over the years of investigation it has been demonstrated that physical functioning and exercise capacity can be improved in these patients when a programme of exercise has been introduced before, during, or after dialysis, improving muscle mass and strength, physical functioning, and health-related quality of life as well as clinical outcomes such as blood pressure control and urea clearance. Sadly, with all this robust data, a standard rehabilitation programme of exercise or referral scheme is yet to be established and only recently a report has shown that two-thirds of haemodialysis patients are frail with an even greater proportion in older and diabetic populations (Johansen et al 2007).

Ultimately the CKD population is seeking an intervention or rehabilitation programme which increases lean body mass, strength, function, health-related quality of life, and reduces the level of exertional fatigue for the patient alongside improved mortality and reduced hospitalization which also hinders the progression of the disease. Performing ADLs competently involves short bursts of activity, often of relatively high intensity. Therefore basing any improvements on measures of exercise capacity and oxygen uptake (such as when implementing an endurance intervention), whilst important, do not truly reflect the functional limitation of the CKD patient. However PRT during dialysis may be limited by equipment and maneuverability and therefore may not provide the stimulus required to affect muscle size, lean body mass, and fat mass. Due to the initial low training loads and volumes, it may be necessary for a longer training session and intervention period for significant adaptation to take place.

Table 2.7a shows studies that have utilized resistance training exercise as an intervention in CKD. Table 2.7b explores the same studies, extracting further detail regarding outcome measures and results.

Table 2.7a - Resistance training intervention studies in Chronic Kidney Disease (ordered by CKD stage and alphabetically by author)

Author, year, journal	study design	CKD stage 1-5	Participant number n (M, F) and further details	intervention type	intensity	when performed	Time/ duration of intervention
PRE (NON) DIALYSIS							
RANDOMISED CONTROLLED TRIALS							
Balakrishnan et al 2010	RCT	CKD 3-4	control 10 (9M, 1F)	control = low protein diet + attention control (flexibility stretches)		supervised @ university	12 weeks
Clin J Am Soc Nephrol 5 (6): 996-1002		"moderate to severe"	Ex 13 (8M, 5F)	ex = low protein diet + 45mins PRT	80% 1RM		3times/ week
linked to Castaneda 2001 and 2004			Total: 64±10yrs Weight 80.7±15.1kg BMI 28.1±4.9	RT 3x8 @80%1RM chest, legpress, lat pulldown, knee extension and flexion, flexibility stretches			
Castaneda et al 2001	RCT	GFR ~27.5ml/ min/1.73m^2					
Annals of Internal Medicine 135(11): 965-76							
Castaneda et al 2004	RCT	pre-dialysis	Ex (RT): 14 (8m,6f) 65±9yrs BMI 29.3±6.6	RT + low protein diet	80% 1RM	supervised at university	12 weeks
American Journal of Kidney Diseases 43 (4): 607-16		"moderate to severe" CKD	Con: 12 (9m,3f) 64±12yrs BMI 26.8±2.7	control: low protein diet (0.6g/kg/day) + attention control exercise/stretches	assessed by RPE		3 times/ week
NON RANDOMISED, CONTROLLED TRIALS							
Heiwe et al 2001	NonRCT (self-selected grouping)	pre-dialysis GFR <= 25ml/ min	CKD exercise n=16 (9m, 7F) 76±7yrs	PRT(3x 20reps) knee extension left, KE right, static endurance of quads (5secs), then 30min low intensity general ex	60% 1RM low weight, high reps	supervised	3 times/ week
Nephron 88: 44-56			CKD control n=9 (6M, 3F) 72±6yrs	control - maintained sedentary lifestyle			12 weeks
Heiwe et al 2005	NonRCT (self-selected grouping)	pre-dialysis GFR <= 25ml/ min	CKD exercise n=7 (4M, 3F) 76±8yrs healthy exercise n=6 (2M, 3F) 71±4yrs	PRT (3x 20reps) knee extension left, KE right, static endurance of quads (5secs), then 30min low intensity general ex	60% 1RM low weight, high reps	supervised	3 times/ week
Am J Phys Med Rehab 84: 865-74			CKD control n=5 (4M, 1F) 71±5yrs	control - maintained sedentary lifestyle			12 weeks

Table 2.7a (continued) – resistance training in CKD

Author, year, journal	study design	CKD stage 1-5	Participant number n (M, F) and further details	intervention type	intensity	when performed	Time/ duration of intervention
DIALYSIS – HD							
RANDOMISED CONTROLLED TRIALS							
Cheema et al 2007a American Society of Nephrology 18: 1594-1601	*for methods : Cheema et al 2006* *Hemodialysis International 10:303-10*		Ex: 24 (17m, 7f) con 25 (17m, 8f) Total: 62.6±14.2yrs Weight 75.7±18.3kgs Height 165.6±10.2cm BMI 27.5±5.8				
Cheema et al 2007b American Journal of Kidney Diseases 50 (4): 574-84	"PEAK study" phase2 randomly assigned to 24wks training, or 12wk control then 12wk training	HD	12 week n=19 24 week n=20			intradialytic	24wks 3 times/ week
Cheema et al 2011 Eur J Appl Physiol 111: 1437-45	RCT "PEAK" study phase 1	HD	Ex (13: 9, 4) control (18: 12, 6) Total : 63.7±14.3yrs Weight 74.8±183.5kg Height 164.4±10.3cm BMI 27.6±5.8	PRT (2x8reps initial load 0-15kg) Control: usual care RT: usual care + shoulder press, side should raise, tricep extension, bicep curl, external shoulder rotation (with free weights), seated knee extension, supine hip flexion, supine hip abduction, supine straight leg raise (with ankle weights), seated hamstring curls (with therabands), bilateral leg raise	RPE 15-17 "high"	intradialytic	12 weeks 3times/ week
Chen et al 2010 Nephrol Dial Transplant 25(6): 1936-43	RCT	HD	control 22 (11M, 11F) 66.9±13.4yrs Dry weight 72.9±±20.8kg BMI 27.7±7.8 Ex 22 (12M,10) 71.1±12.6yrs Dry weight 71.2±17.7kg BMI 25.7±7.1	control: attention control flexibility stretches RT: 2x8reps ankle weights, lower body exercise only: 0.5lbs-20lbs	aim *moderate* on modified RPE (6/10) ~60%1RM actual RPE <6	intradialytic	48 sessions (24 wks) twice/week
DePaul et al 2002 Am J Kidney Disease 40 (6): 1219-29 (abstract only)	RCT	HD		progressive resistance isotonic exercise on a cycle ergometer control: non-progressive range of motion exercise			12 weeks 3 times/ week
Dong et al 2011 J Ren Nutr 21 (2): 149-59	RCT	HD	Con 17 (12m,5f) Ex 15 (9m,6f) Total: n=32 43.2±13.1yrs BMI 28.4±6.3	Control = nutritional high protein drink Ex = drink + PRT RT: 3x12reps leg press @ 70% 1RM	70% 1RM	30-mins pre-dialysis	6 months every dialysis session ~3/wk

Table 2.7a (continued) – resistance training in CKD

Author, year, journal	study design	CKD stage 1-5	Participant number n (M, F) and further details	intervention type	intensity	when performed	Time/ duration of intervention
DIALYSIS – HD							
RANDOMISED CONTROLLED TRIALS							
Johansen et al 2006 Journal of the American Society of Nephrology 17: 2307-14	RCT	HD	79 (49m,30f) 56±13yrs (range 26-88yrs) control1: placebo n=20 (14,6) experimental 1: nandrolone n=19 (10,9) control2: RT n=20 (12,8) experimental 2: nandrolone + RT n=20 (13,7)	weekly injection placebo weekly injection of nandrolone decanoate (M200mg, F100mg) knee extension, hip abduction, hip flexion, ankle dorsi and plantar flexion 2x 10reps --> 3x10reps nandrolone + RT	 60% 3RM 60% 3RM	intradialytic supervised	12 weeks 3 times/ week
Oliveros et al 2011 Rev Med Chil 139 (8): 1046-53 Spanish *translated in google*	RCT (pilot study)	HD	Ex (5: 5,0) 46±13yrs Dry weight 74.5±5.5kg control (6: 3,3) 52.2±17yrs Dry weight 73.3±9.3kg	Combination: Aerobic (20-25mins) : continuous pedalling RT (20-25 mins): therabands, knee extn uni and bilaterally	moderate 40-60%HRR (aerobic) use Borg RPE 13	intradialytic	16 weeks 3times/ week
Orcy et al 2012 Physiotherapy Research International 17: 235-43	RCT	HD	RT: n=13m 55.8±18.3yrs BMI 25.3±2.7 RT+aerobic: n=13 (9m,4f) 56.9±14.8yrs BMI 23.9±3.5	RT: 30mins RT; twice through elbow flexors, shoulder flexors, hip flexors, hip abductors, hamstrings; 2x10-15reps. 30mins RT; elbow flexors, shoulder flexors, hip flexors, hip abductors, hamstrings; 2x10-15reps.	subjective perception	during dialysis	10 weeks

Table 2.7a (continued) – resistance training in CKD

Author, year, journal	study design	CKD stage 1-5	Participant number n (M, F) and further details	intervention type	intensity	when performed	Time/ duration of intervention
DIALYSIS – HD							
RANDOMISED CONTROLLED TRIALS							
Segura-Orti et al 2009 Clinical Nephrology 71 (5): 527-37	RCT control/ placebo = low intensity aerobic	HD	Total: 55.6±17.6yrs A (RT): 17 (11m,6f) Dry weight 64.9±13kg BMI 24.6±2.6 B (Aero/ control): 8 (7m,1f) Dry weight 72.4±7.8kg BMI 24.9±2.2	RT 4 progressive exercises: knee extension, unilateral triple extension (hip, knee, ankle) 3 x 15 reps isometric contraction of ankle flexors, quads, hip extensor Aero /placebo: stationary bike continuous cycling	RPE 12-14 RPE 11	intradialytic supervised	24 weeks/ 6months 3 times/ week
Song & Sohng 2012 J Korean Acad Nurs 42 (7): 947-56	RCT	HD	PRT n=20 (8m,12f) 52.1±12.4yrs (range 31-74yrs) Dry weight 54.9±5kg Control n=20 (12m,8f) 54.6±10.1yrs (range 37-70yrs) Dry weight 57±9.6kg	PRT vs usual care PRT (3 x 10-15 reps): 6upper body and 6 lower body strengthening exercises - therabands and ankle sandbags	RPE 11-15	in waiting time for dialysis	12 weeks 30min 3/week
Van Vilsteren et al 2005 Nephrol Dial Transplant 20: 141-6	RCT	HD	96 total Ex: 5363%M 52±15yrs Con: 43 70%M 58±16yrs	RT + aero vs usual care 5-10min warm up, 20min exercise (calisthenics, steps, flexibility, low weight resistance), 5-10min cool down	RPE 12-16 "low-moderate " ~60% max	pre-dialysis RT + intradialytic aerobic	12 weeks 2-3 times/ week
NON-RANDOMISED, CONTROLLED TRIALS							
Segura-Orti et al 2008 Nefrologia 28 (1): 67-72(abstract)	nonRCT Self-selected grouping	ESRD/ HD	Ex : 8 Control: 8	RT isometric and isotonic exercises on lower limbs		intradialytic supervised	6 months

Table 2.7a (continued) – resistance training in CKD

Author, year, journal	study design	CKD stage 1-5	Participant number n (M, F) and further details	intervention type	intensity	when performed	Time/ duration of intervention
DIALYSIS – HD							
CROSSOVER AND SELF-CONTROLLED TRIALS							
Headley et al 2002	crossover/ self-controlled	HD	10 (7M, 3F) 42.8±4.4yrs (range 24-67yrs)	PRT	RPE<=15	supervised + one session unsupervised	12 weeks
Am J of Kidney Disease 40 (2): 355-64	6wks control/ no intervention		Height range 156.2-182.9cm Weight 90±4.9kg (range 63.5-123.9kg)	1x10 --> 3 x 15reps	if RPE dropped to 10-12, added weight		2/week + 1/week theraband at home
MacDonald et al 2005	self-controlled (pilot study)	HD	9 (7m, 2f)	High intensity interval training	"high" RPE > 17 during intense bouts	intra-dialytic	12 weeks
Clin Physiol Funct Imaging 25: 113-8	12-weeks pre-intervention - 12-week intervention			2-min intensive cycling, 2-min active recovery, 15 times	RPE ~ 7 for active recovery		3 times/ week (min of 36 sessions)
Nindl et al 2004 Growth Hormone & IGF Research 14 (3): 245-50	Self-controlled (6wks prior to baseline measures)	HD	7M,3F 42.8±144.5yrs Height 172.7±10.1cm Weight 90±15.6kg	9 strength exercise using machines: double leg press, leg extension, leg curl, chest press, compound row, lateral raise, bicep curl, tricep extension, abdominal curl			
NO CONTROL							
Bullani et al 2011 Journal of Renal Nutrition 21 (1): 61-65	no control group (pilot study)	HD	11 (8m, 3F) 70±10.7yrs (range 53-84yrs)	PRT - 3x20reps "moderate intensity" foot extension, knee extension, hip flexion and extension using elastic resistance bands	moderate	intradialytic supervised	2/week 4.5-6months total of 36 sessions

Presented as mean ± standard deviation unless otherwise stated; IQR = interquartile range; SEM = standard error of the mean; SE = standard error; RCT = randomised controlled trial; nonRCT = non randomised controlled trial; Xover = crossover design; exp = experimental group; co/con = control group; pla = placebo group; MTH = muscle thickness; VL = vastus lateralis; CSA = cross sectional area; PRT = progressive resistance training; 2-D = 2-dimensional; US = ultrasound or ultrasonography; ns = non-significant result; HD = haemodialysis treatment; PD = peritoneal dialysis treatment; ESRD = end-stage renal disease; CT = computed tomography; DEXA = dual energy x-ray absorptiometry; MAMA = mid-arm muscle area; TSF = total skinfold; BIA = bioelectrical impedance analysis; CKD1…5 = stage of disease (1-5); RPE = rate of perceived exertion

2.7.5.1 Limitations in design of these resistance training (RT) studies (Table 2.7a)

As with the non-exercise CKD studies, the majority of research has been conducted using patients already undergoing dialysis; HD (17), PD (0), mixed stage (0), pre-dialysis (5). The few studies of resistance training in pre-dialysis/non-dialysis have combined exercise with a change in diet (Castaneda 2001, 2004; Balakrishnan 2010), so whether the effect was limited by the lack of protein in the diet is unclear as there may be a greater/more significant effect when diet is uncontrolled, or at least be easier to implement. The other pre-dialysis studies used low weight with high repetitions which could be classed as more aerobic than purely strength (resistance) training (Heiwe 2001, 2005). Heiwe (2001 and 2005) also did not randomize the groups (self-selected/ nonRCT).

From these studies an additional question has arisen: as there is no information regarding different frequency of training; most studies (dialysis and pre-dialysis) implemented the training intervention three times per week compared to a control group as standard; is that volume of training necessary for statistically and clinically relevant results?

2.7.5.2 Limitations in outcomes and results of these RT studies (Table 2.7b)

Outcome measures predominantly examined body composition and strength with some functional measures, however there is little information on the clinical implications in the non/pre-dialysis studies (eg. health-related quality of life, or change in symptoms prevalence or intensity), though they were often reported in dialysis (HD) studies.

RCTs in dialysis show mixed results. Measures of muscle strength reported no significant difference after training in two studies (Segura-Orti 2009; Headley 2002) compared to a highly significant ($p<0.01$) improvement in another (Cheema 2011). Body composition (muscle mass) assessments showed similar inconsistencies as three studies again found no significant difference in muscle size after training

(MacDonald 2005; Dong 2011; Cheema 2011) compared to two studies demonstrating highly significant ($p<0.01$) improvements (Song & Sohng 2012; Chen 2010), with varying levels of significance for both positive and negative change in other studies.

In comparison, despite there being fewer studies in pre/non-dialysis patients, similar exercise interventions (to those in HD patients) have brought about highly significant improvements in strength (Castaneda 2004; Heiwe 2001, 2005) suggesting that the effect is smaller when intervening in patients already in dialysis compared to those non-dialysis (NDD) patients.

In this selection of studies (tables 2.7a and 2.7b) it would also appear that combining resistance (strength) training with aerobic (endurance) training seems to have a negative effect on strength outcome measures (Van Vilsteren 2005), or impose a non-significant limitation (Oliveros 2011).

Table 2.7b – Resistance training studies in CKD (outcome measures and results)

Author, year, journal	Mode of assessment	pre intervention/ baseline values	post intervention values	actual change reported	% change if reported	significance (p)	group difference (p)
PRE (NON) DIALYSIS							
RANDOMISED CONTROLLED TRIALS							
Balakrishnan et al 2010	vastus lateralis biopsy: MtDNA					Ex: +1306 p=0.22 (ns)	p=0.001
Clin J Am Soc Nephrol 5 (6): 996-1002 *linked to Castaneda 2001 and 2004*						Co: -3747 p=0.04	
Castaneda et al 2004	dietary compliance (% of prescription)		108 ± 8				
American Journal of Kidney Diseases 43 (4): 607-16	body weight kg	84.6 ± 15.8	84.8 ± 16.2	0.2 ± 2.6			0.049
AND Castaneda et al 2001	type I muscle fibre area um2	3887 ± 1566	4821 ± 1411	934 ± 1486	24 ± 31		0.031
Annals of Internal	type II muscle fibre area um2	3626 ± 1216	4437 ± 1393	811 ± 1479	22 ± 29		0.045
Medicine	muscle strength kg	298 ± 106	384 ± 123	86 ± 45			0.001
135(11): 965-76	c-reactive protein mg/L	7.8	6.1	-1.7			0.049
	serum il-6 (pg/ml)	11.3	6.9	-4.2			0.012
	serum transferrin (mg/dl)	178 ± 32	258 ± 52	80 ± 25			0.042
	serum albumin (g/dl)	3.7 ± 0.3	3.8 ± 0.2	0.1 ± 0.2			0.091 (ns)
	relationship total body potassium and muscle strength				r=0.36	0.05	
	relationship il-6 and crp				r=0.46	0.04	
	relationship il-6 and type I fibres				r=-0.58	0.02	
	relationship il-6 and type II fibres				r=-0.68	0.005	
	relationship il-6 and muscle strength				r=-0.49	0.05	
	relationship crp and muscle strength				r=-0.45	0.03	
	relationship crp and serum albumin				r=-0.47	0.05	
	adherence to training		91 ± 9				
	GFR ml/min/1.73m2	24.76	26.35	1.18			0.048
	chest press kg	24.0 ± 10.4	31.8 ± 12.9		34 ± 12		<0.001
	lat pulldown kg	26.4 ± 7.5	33.9 ± 10.0		29 ± 14		<0.001
	leg press kg	167.4 ± 102.3	210.9 ± 129.0		29 ± 15		0.001
	knee extension kg	39.9 ± 17.8	55.9 ± 22.4		47 ± 24		<0.001
	knee flexion kg	39.8 ± 13.6	55.8 ± 13.6		44 ± 22		<0.001
	total body potassium kg	101.6 ± 25.2	105.8 ± 23.9	1.9 ± 7.9	4 ± 8		0.014
	mid-thigh muscle area cm2	108.9 ± 29.5	111.3 ± 29.6	2.42 ± 8.35			0.113 (ns)
NON-RANDOMISED, CONTROLLED TRIALS							
Heiwe et al 2001	knee ext strength 1RMkg	8 ± 5	13 ± 5			<0.0001	
Nephron 88: 44-56	quad dynamic musc endurance, reps	37 (14-57)	48 (30-101)			0.004	
	quad static musc endurance, secs	28 (12-60)	32 (15-150)			ns	
	6MWT m	390 ± 128	452 ± 99			0.002	
	TUG secs	11 (9-46)	9 (7-27)			0.004	

Table 2.7b (continued) – RT in CKD (outcome measures)

Author, year, journal	Mode of assessment	pre intervention/ baseline values	post intervention values	actual change reported	% change if reported	significance (p)	group difference (p)
PRE (NON) DIALYSIS							
RANDOMISED CONTROLLED TRIALS							
Heiwe et al 2005	knee ext strength 1RM kg	5 (3-12.5)	7 (5-12)			0.0104	
Am J Phys Med Rehab 84:	quadricep static endurance, reps	37 (28-57)	55 (43-101)			ns	
865-74	muscle fibre area					ns	ns
	muscle fibre proportion					ns	ns
DIALYSIS - HD							
RANDOMISED CONTROLLED TRIALS							
Cheema et al 2007a	CT mid-thigh muscle CSA cm2	104.2 ± 25.6		1.2 ± 5.8			0.4 (ns)
American Society of	CT mid-thigh muscle attenuation	85.7 ± 2.5		- 0.1 ± 0.9			0.04
Nephrology 18:	CT mid-thigh fat cm2	73.8 ± 35.1		0.9 ± 7.7			0.95 (ns)
1594-1601	CT mid-thigh subcut fat cm2	61.7 ± 27.5		0.5 ± 7.2			0.93 (ns)
Cheema et al 2006	strength kg (sum 3 measures: knee ext, tri, hip abductors)	98.1 ± 36.6		15.2 ± 15.4			0.002
Hemodialysis	6MWT m	496.6 ± 133.3		16.7 ± 40.5			0.16 (ns)
International	mid-thigh circumf cm	47.5 ± 6.0		0.7 ± 1.1			0.04
10:303-10	mid arm circumf cm	30.1 ± 4.0		0.4 ± 1.4			0.004
for methods	mid-calf circumf cm	35.3 ± 3.8		0.2 ± 1.2			0.41 (ns)
	SF36 physical function (0-100)	73.5 ± 26.3		7.6 ± 11.8			0.02
	SF36 vitality (0-100)	57.7 ± 22.2		2.8 ± 16.3			0.02
	geriatric depression scale (0-30)	7.2 ± 7.1		- 0.3 ± 3.6			0.11 (ns)
Cheema et al	adherence/compliance		76.5 ± 22.2				
2007b	CT mid-thigh muscle CSA cm2	103.11 ± 23.81		1.82 ± 3.25			0.04
American Journal of	CT mid-thigh muscle attenuation	85.56 ± 2.70		0.19 ± 1.32			0.31 (ns)
Kidney Diseases	KE strength kg	45.1 ± 19.5		13.8 ± 16.1		<0.001	0.36 (ns)
50 (4): 574-84	hip abduction strength kg	22.3 ± 8.8		6.8 ± 3.8		<0.001	0.09 (ns)
	tricep strength kg	27.8 ± 11.6		5.6 ± 7.7		0.002	0.17 (ns)
	strength kg (sum 3 measures: knee ext, tri, hip abductors)	95.2 ± 35.3		26.2 ± 21.3		<0.001	0.34 (ns)
	specific tension kg/cm2	0.22 ± 0.08		0.07 ± 0.08		0.003	0.34 (ns)
	6MWT m	496.0 ± 138.9		36.3 ± 50.6		<0.001	0.53 (ns)
	mid arm circumf cm	29.9 ± 3.8		0.6 ± 2.0			0.36 (ns)
	mid-calf circumf cm	35.0 ± 3.8		0.5 ± 1.0			0.34 (ns)

Table 2.7b (continued) – RT in CKD (outcome measures)

Author, year, journal	Mode of assessment	pre intervention/ baseline values	post intervention values	actual change reported	% change if reported	significance (p)	group difference (p)
DIALYSIS - HD							
RANDOMISED CONTROLLED TRIALS							
Cheema et al	compliance/adherence		85 ± 14 %				
2011	il-1B (pg/ml)	2.0 ± 1.5		0.5		ns	ns
Eur J Appl	il-6 (pg/ml)	7.2 range (3.4-18.5)		7.5 range (3.4-17.2)		ns	ns
Physiol 111: 1437-45	il-8 (pg/ml)	18.1 range (13.2-152.9)		23.7 range (12.2-209.6)		ns	ns
	il-10 (pg/ml)	2.1 range (0-8.9)		2.2 range (0-18.1)		ns	ns
	il-12 (pg/ml)	2.5 ± 1.3		0.2		ns	ns
	tnf-a (pg/ml)	1.8 ± 1.0		1.1		ns	ns
	relationship thigh muscle csa and il-6				r=-0.49	0.008	
	relationship thigh fat and il-6				r=-0.43	0.03	
	relationship thigh subcut and il-6				r=-0.52	0.01	
	relationship thigh subcut fat and il-8				row= -0.42	0.05	
Chen et al 2010	Short Physical Performance Battery Score (SPPB)	5.0 IQR(5.2)	7.0 IQR(7.2)		21.1 IQR(43.1)		0.03
Nephrol Dial Transplant	SPPB score change due to STS5				-16.4 ± 43.3		0.04
25(6): 1936-43	knee extensor strength kg	11.4 ± 5.0	15.8 ± 5.0		44.9 ± 26.3		0.0001
	DEXA whole body lean mass kg	45.8 ± 8.9	47.9 ± 9.9		4.2 ± 5.6		0.0001
	DEXA leg lean mass kg	6.9 ± 1.7	7.2 ± 2.0		5.0 ± 7.6		0.0001
	DEXA whole body fat mass %	31.3 ± 10.4	29.6 ± 9.8		-2.6 ± 16.9		0.02
	HRQoL PhysActivity (PASE) score	47.5 IQR(45.9)	57.5 IR(69.3)		10.3 IQR(88.1)		0.0001
	HRQoL SF36 physical score	46 ± 12	54 ± 12		21 ± 36		0.02
	HRQoL SF36 mental score	37 ± 11	37 ± 9		6 ± 27		ns
	ADL disability summary score	6.3 ± 0.9	7.0 ± 1.4		10.5 ± 21.1		0.02
	adherence/compliance		85 ±15 %				
DePaul et al 2002	submaximal exercise test (W)			14 (CI, 2-26)		<0.05	
Am J Kidney	muscle strength (lbs)			45 (CI, 9-81)		<0.05	
Disease 40 (6):	6MWT					ns	
1219-29	SF36					ns	
(abstract only)	symptoms score					ns	

Table 2.7b (continued) – RT in CKD (outcome measures)

Author, year, journal	Mode of assessment	pre intervention/ baseline values	post intervention values	actual change reported	% change if reported	significance (p)	group difference (p)
DIALYSIS - HD							
RANDOMISED CONTROLLED TRIALS							
Dong et al 2011	Strength - 1 RM leg press lbs	459 ± 117	582 ± 147	all cohort p=0.001 +84lbs			t3 p=0.07 (ns) t6 p=0.12 (ns)
J Ren Nutr 21 (2): 149-59	body composition by BIA and DEXA			all cohort body weight p=0.02 +0.6kg			all other measures NS
	Subjective Global Assessment - 7 scale method	n=13/15	n=9/10			ns	ns
	c-reactive protein (mg/L)	4.3 IQR(1.9, 13.3)	2.6 IQR(1.3, 8.3)			ns	ns
	adherence/compliance		LP weight: 71-82% success attendance "excellent"				
Johansen et al 2006	adherence to training		89 ± 8				
Journal of the	**RT+nandrolone**						
American	body weight kg	73.2 ± 23.1	75.1 ± 23.0	1.8 ± 2.9			
Society of	lean body mass kg	47.2 ± 14.4	50.1 ± 15.1	3.0 ± 2.4			
Nephrology 17:	fat kg	19.2 ± 8.3	18.6 ± 7.9	- 0.6 ± 1.1			
2307-14	quadriceps csa cm2	39.5 ± 9.3	46.2 ± 12.7	6.7 ± 5.3			0.43 (ns)
	strength KE 3RM lbs	16.7 ± 8.7	24.9 ± 8.4	8.2 ± 6.2			
	strength hip abduction 3RM lbs	10.3 ± 4.6	18.1 ± 6.0	7.8 ± 4.6			
	strength hip flexion 3RM lbs	9.7 ± 4.7	16.9 ± 8.3	7.2 ± 5.5			
	isokinetic KE@90 Nm	43.6 ± 26.9	49.9 ± 27.8	6.3 ± 11.0			
	isokinetic KE@120 Nm	35.5 ± 23.2	45.6 ± 26.2	10.2 ± 9.7			
	HRQoL SF36 physical score	49.7 ± 26.9	56.3 ± 30.6	6.6 ± 10.8			
	nandrolone alone						
	body weight kg	64.0 ± 12.9	66.5 ± 13.5	2.5 ± 3.5		0.04	
	lean body mass kg	45.7 ± 9.3	49.0 ± 9.0	3.3 ± 2.0		<0.0001	
	fat kg	16.4 ± 13.6	15.8 ± 14.1	- 0.7 ± 1.8		0.0009	
	quadriceps csa cm2	46.6 ± 15.7	50.9 ± 16.9	4.2 ± 4.3		<0.0001	
	strength KE 3RM lbs	13.0 ± 7.1	14.4 ± 7.3	1.4 ± 2.3		0.99 (ns)	
	strength hip abduction 3RM lbs	9.1 ± 6.0	9.2 ± 6.3	0.1 ± 2.2		0.66 (ns)	
	strength hip flexion 3RM lbs	6.4 ± 6.1	7.4 ± 6.6	1.0 ± 2.5		0.41 (ns)	
	isokinetic KE@90 Nm	30.7 ± 22.4	41.3 ± 26.3	10.6 ± 23.9		0.36 (ns)	
	isokinetic KE@120 Nm	33.3 ± 27.5	39.5 ± 30.6	6.2 ± 14.1		0.38 (ns)	
	HRQoL SF36 physical score	55.4 ± 34.7	58.9 ± 29.7	3.6 ± 10.1		0.63 (ns)	
	RT alone						
	body weight kg	76.5 ± 21.5	78.0 ± 21.3	1.6 ± 2.0		0.51 (ns)	
	lean body mass kg	47.5 ± 12.3	47.1 ± 11.2	- 0.3 ± 3.0		0.66 (ns)	
	fat kg	22.4 ± 11.3	24.5 ± 11.1	2.2 ± 2.9		0.05	
	quadriceps csa cm2	47.9 ± 13.9	49.1 ± 13.5	1.2 ± 4.0		0.02	
	strength KE 3RM lbs	14.0 ± 8.4	22.6 ± 11.6	8.6 ± 6.9		<0.0001	
	strength hip abduction 3RM lbs	8.5 ± 5.2	15.4 ± 6.9	6.9 ± 5.0		<0.0001	
	strength hip flexion 3RM lbs	7.6 ± 5.3	13.7 ± 6.8	6.1 ± 4.3		<0.0001	
	isokinetic KE@90 Nm	39.2 ± 25.1	46.8 ± 28.9	7.6 ± 12.3		0.77 (ns)	
	isokinetic KE@120 Nm	35.1 ± 23.9	43.9 ± 26.1	8.8 ± 12.4		0.08 (ns)	
	HRQoL SF36 physical score	50.0 ± 24.7	61.5 ± 30.8	11.5 ± 15.4		0.03	

Table 2.7b (continued) – RT in CKD (outcome measures)

Author, year, journal	Mode of assessment	pre intervention/ baseline values	post intervention values	actual change reported	% change if reported	significance (p)	group difference (p)
DIALYSIS - HD							
RANDOMISED CONTROLLED TRIALS							
Oliveros et al 2011	6MWT (metres)	596 ± 79	630 ± 85	34.4		0.05	0.037
Rev Med Chil 139 (8): 1046-53	Quad strength - right leg (kg)	15.4 ± 5	19.3 ± 3.9	3.86		0.03	0.027
Spanish *translated in*	Quad strength - left leg (kg)	18 ± 4.4	21 ± 4	3		0.02	0.054 (ns)
google	HRQoL (SF-36)					ns	ns
	Depression (Beck BDI-I)	10.6 ± 4.9	13.4 ± 8.0			ns	ns
	c-reactive protein (hsCRP) pre-dialysis (mg/L)	6.2 range (5.3-12.3)	6.2 range (5.4-7.4)			ns	ns
	IL-6 (pg/ml) pre-dialysis	3.77 range (2.76-22.6)	4.95 range (2.51-5.04)			ns	ns
	TNF-a (pg/ml) pre-dialysis	19 range (17-22.2)	18.7 range (14.8-29.7)			ns	ns
Orcy et al 2012	RT alone: 6MWT	431.0 ± 108.7	411.7 ± 113.6	- 19.3 ± 53.9		0.24 (ns)	0.02
Physiotherapy Research	RT alone: adherence to training %		85 ± 12				
International 17	combi: 6MWT	440.5 ± 108.8	480.2 ± 108.7	39.7 ± 61.4		0.04	
235-43	combi: adherence to training %		72 ± 15				
Segura-Orti et al 2009	adherence/compliance		80.1				
Clinical	STS10 (secs)	24.2 ± 13.2	18.8 ± 7.9	- 5.4 ± 10.6	22.3	ns	0.003
Nephrology 71	STS60 (count)	28.8 ± 11.2	33.9 ± 12.6	5.1 ± 5.8	17.7	0.05	0.0005
(5): 527-37	6MWT (metres)	432.5 ± 109.3	481.0 ± 100.3	48.5 ± 60.8	11.2	0.01	0.003
	right leg peak force (kg) knee extensor @90	25.2 ± 9.3	27.9 ± 9.4	1.5 ± 4.2		ns	ns
	left leg peak force (kg) knee extension @90	25.4 ± 10.2	28.0 ± 10.1	1.2 ± 4.6		ns	ns
	graded exercise test/ Bruce protocol (mins)	4.9 ± 2.3	5.8 ± 2.7	1.0 ± 1.8		ns	ns
	graded exercise test/ Bruce protocol (METS)	5.7 ± 2.0	6.6 ± 2.7	0.9 ± 1.9		0.043	ns
	HRQoL (SF-36) physical	42.7 ± 8.4	44.7 ± 8.7			ns	ns
	HRQoL (SF-36) mental	45.1 ± 9.7	46.5 ± 13.5			ns	ns
Song & Sohng 2012	participation rate in PRT %		88				
J Korean Acad	skeletal muscle mass	21.4 ± 3.6	22.2 ± 3.7	0.8 ± 1.0			0.002
Nurs 42 (7):	body fat %	27.5 ± 9.4	26.0 ± 8.9	- 1.5 ± 3.7			0.02
947-56	grip strength kg	26.3 ± 8.5	28.7 ± 9.0	2.4 ± 2.8			0.465 (ns)
	leg muscle strength kg	33.0 ± 15.3	37.3 ± 19.0	4.3 ± 8.7			0.027
	sit up (count over 30secs)	7.9 ± 7.3	8.2 ± 7.7	0.4 ± 2.0			0.754 (ns)
	balance (secs)	7.4 ± 12.0	7.9 ± 15.0	0.6 ±8.2			0.967 (ns)
	quality of life - physical component	64.5 ± 13.0	72.5 ± 9.8	7.9 ± 9.9			0.002
	quality of life - mental component	62.9 ± 15.9	69.4 ± 13.7	6.5 ± 11.6			0.014
	total cholesterol (mg/dL)	163.8 ± 31.0	148.7 ± 26.2	- 15.1 ± 31.1			0.017
	triglycerides (mg/dL)	143.6 ± 88.1	118.3 ± 63.3	- 25.3 ± 62.4			0.012

Table 2.7b (continued) – RT in CKD (outcome measures)

Author, year, journal	Mode of assessment	pre intervention/ baseline values	post intervention values	actual change reported	% change if reported	significance (p)	group difference (p)
DIALYSIS - HD							
RANDOMISED CONTROLLED TRIALS							
Van Vilsteren et al 2005	completion of programme %		88				
Nephrol Dial	reaction time (ms)	234.67 ± 43.9	208.51 ± 36.0			0.002	
Transplant 20:	muscle strength	26.3 ± 14.6	20.42 ± 7.5			0.05	
141-6	SF36 - physical functioning	56.5 ± 28.0	62.5 ± 28.0			0.22 (ns)	
	SF36 - mental health	72.1 ± 17.4	76.2 ± 18.9			0.20 (ns)	
	SF36 - vitality	53.6 ± 16.8	66.1 ± 15.3			0.001	
	SF36 - general health perception	41.3 ± 19.2	51.8 ± 15.9			0.001	
	SF36 - health change	50.0 ± 24.4	67.1 ± 26.0			0.021	
	SF36 - symptom score	22.5 ± 8.6	23.5 ± 9.1			0.06 (ns)	
NON-RANDOMISED, CONTROLLED TRIALS							
Segura-Orti et al 2008	6MWT	399.57 ± 39.56	471.71 ± 70.63			<0.01	
Nefrologia 28	STS10 (secs)	22.52 ± 4.77	17.71 ± 1.79			<0.05	
(1): 67-72	STS60 (count)	28.57 ± 5.12	31.42 ± 2.443			<0.05	
(abstract)	HRQOL (SF36) physical						
	HRQOL (SF36) mental	41.74 ± 9.25	50.61 ± 12.13			<0.05	<0.05
CROSSOVER AND SELF-CONTROLLED TRIALS							
Headley et al 2002	attendance %		87.7 ± 11.6				
Am J of Kidney Disease 40 (2): 355-64	skinfold thicknesses fat (%)	18.8 ± 2.0	19.6 ± 1.7			<0.05	<0.05
MacDonald et al 2005	work done per session (kpm)	2336.7 ± 548.6	8728.9 ± 1571.0			<0.001	
Clin Physiol	DEXA fat mass kg	20.3 ± 3.7	20.8 ± 3.7			ns	ns
Funct Imaging	DEXA lean mass kg	48.3 ± 3.0	47.8 ± 3.2			ns	ns
25: 113-8	BIA ICW litres	19.9 ± 1.9	19.7 ± 1.7			ns	ns
	BIA ECW litres	16.4 ± 1.0	15.3 ± 1.2			<0.05	<0.05
	Sit to stand 30	~11.5	~13.5		20	<0.05	<0.05
	knee extension N	23.5 ± 4.2	28.0 ± 4.0		19	<0.05	<0.05
Nindl et al 2004	leg extension peak force 90	123.5 ± 16.9	139.1 ± 19.3		12.7 ± 3.6	<0.05	<0.05
Growth Hormone & IGF Research	leg extension peak force 120	111.9 ± 14.8	121.8 ± 19.1			ns	ns
14 (3): 245-50	leg extension peak force 150	101.8 ± 18.0	107.3 ± 20.1			ns	ns
	grip strength right kg	40.0 ± 4.7	40.7 ± 4.7			ns	ns
	grip strength left kg	37.7 ± 4.7	39.3 ± 4.9			ns	ns
	6MWT	521.9 ± 48.5	546.5 ± 54.2			<0.05	<0.05
	gait speed 20ft - normal cm/s	132.4 ± 7.1	131.3 ± 8.1			ns	ns
	gait speed 20ft - max	185.5 ± 13.0	195.9 ± 15.4			<0.05	<0.05
	STS 10	20.6 ± 1.8	17.8 ± 1.9			<0.05	<0.05
	Total IGF-I ng/ml	320.2 ± 136.5	267.1 ± 129.5			0.039	<0.05
	Ternary IGF-I	25.3±123.6	206.2 ± 115.4			0.048	<0.05
	IGF-I/ IGFBP-3 (x10) ratio	4.83 ± 1.49	3.72 ± 1.72			0.003	<0.05
NO CONTROL							
Bullani et al 2011	Tinetti score	23.9 ± 3.9	25.7 ± 3.5			0.022	
Journal of Renal	TUG secs	12.1 ± 6.6	10.0 ± 5.8			0.0156	
Nutrition 21 (1):	One-leg balance secs	15.7 ± 17.8	21.6 ± 21.6			0.084 (ns)	
61-65	6MWT m	307 ± 155	351 ± 176		14.5	0.0639 (ns)	

Presented as mean ± standard deviation unless otherwise stated; IQR = interquartile range; SEM = standard error of the mean; SE = standard error; RCT = randomised controlled trial; nonRCT = non randomised controlled trial; Xover = crossover design; exp = experimental group; co/con = control group; pla = placebo group; MTH = muscle thickness; VL = vastus lateralis; CSA = cross sectional area; PRT = progressive resistance training; 2-D = 2-dimensional; US = ultrasound or ultrasonography; ns = non-significant result; HD = haemodialysis treatment; PD = peritoneal dialysis treatment; ESRD = end-stage renal disease; CT = computed tomography; DEXA = dual energy x-ray absorptiometry; MAMA = mid-arm muscle area; TSF = total skinfold; BIA = bioelectrical impedance analysis; CKD1…5 = stage of disease (1-5); RPE = rate of perceived exertion

2.8 Early Interventions for improving body composition, strength and function, alongside general well-being and health-related quality of life in CKD

Exercise training in the general population can increase exercise capacity, strength, and health-related quality of life, control or reduce hypertension and diabetes, and increase survival rate (Mendes et al 2011; Zwolinsky et al 2013). The high prevalence of co-morbidities in the renal disease population (such as diabetes, cardiovascular disease, obesity, and ageing) would therefore indicate the importance of exercise training and/or regular physical activity in this population to reduce the burden of disease on each individual. Dialysis patients also have a severe lack of muscular strength highlighted particularly in a study on a more elderly and debilitated dialysis population (Painter et al 2000). Training to avoid muscular atrophy, and encourage hypertrophy, is important in an elderly population, as knee extensor strength has been shown to be inversely related to risk of falling in both healthy and chronically ill populations. Results of baseline physical functioning (sit-to-stand-to-sit test) averaged only 15% of normal age-predicted values (Painter et al 2000).

It can be theorized that this lack of strength is due to denervation from uraemia and/or disuse and any initial increases in strength could be due to improved neuromuscular activation as is expected in healthy resistance training subjects. However, deconditioning and atrophy is thought to start early in the process of chronic renal failure, and often continues following renal transplantation, (Kettner-Melsheimer et al 1987; Miller et al 2002), supporting evidence that a form of training to hinder muscle atrophy is required from onset of the disease process. Unfortunately, the focus of care seems to be on disease management, not prevention, and as such exercise is under-used as a therapeutic tool.

2.8.1 Pre-dialysis

Most studies focus on haemodialysis patients (43% of all UK patients using HD out of the total number requiring RRT; Renal Registry Report, 2013), despite this sub-group making up only a small fraction of the total number of patients with CKD (4% risk of progression to ESRD over a 5.5 year follow-up period, Drey et al 2003; 5-10% total population of kidney disease patients, Renal Registry Report). It is CKD stages 2-4 (pre-dialysis) that actually make up the majority of patients with the disease (Table 2.1).

Exertional fatigue (increased sense of effort in relation to performing a task) is present in patients with moderate CKD, with greater contribution from anaerobic processes (increased lactate production and respiratory exchange ratio) to energy production when undertaking simulations of activities of daily living (CKD3b and CKD4; MacDonald et al 2012), suggesting that already at this level there is a limitation to oxygen delivery, extraction or utilisation.

Previous papers have shown normal oxygen utilization in CKD through mitochondrial function (Thompson et al 1994, Barany et al 1991, Miro et al 2002), so indicating that decreased oxygen delivery alongside a lack of compensatory increased cardiac output (as with healthy individuals), leads to increased use of

anaerobic processes, increased lactate production, greater muscular fatigue and perceived exertion during submaximal ADLs (MacDonald et al 2012). Increasing oxygen extraction to compensate for the reduced oxygen delivery may also be limited in this population as the mitochondrial mass is often reduced (Shah et al 2009; MacDonald et al 2012) by the muscle atrophy and deconditioning observed early on in the disease process (Kettner-Melsheimer et al 1987; Miller 2002), supporting evidence that a form of resistance training to hinder muscle atrophy is required from onset (increased mitochondrial content in skeletal muscle following 12-weeks of resistance training; Balakrishnan et al 2010).

Poor lipid profiles in rat models have been implicated in the progression of CKD (Scheuer et al 2000), and improvements in renal function have been demonstrated after exercise training to treat hyperlipidaemia in nephritic rats (Osato et al 1990). Studies of CKD3 patients undertaking endurance training have also shown improvements in GFR associated with increased HDL, and decreased LDL and TAG (Toyama et al 2010), though not all studies have found an endurance exercise intervention improves the profile and GFR (Headley et al 2012, Boyce et al 1997, Eidemak et al 1997). This may be due to the lack of intensity high enough to elicit a change in the blood lipid and haematology variables.

Improved (reduced) HR at rest and during ambulation has been seen following these endurance interventions, as would be expected based on the normal exercise response in healthy individuals, with HR recovery data suggesting an enhancement of parasympathetic tone, a decrease in sympathetic tone, or a combination of both (Headley et al 2012). A recent study has shown a link between elevated resting HR and low HR variability with increased risk of ESRD and CKD-related hospitalization (Brotman et al 2010).

Ideally, training should begin as soon as possible, commencing in the pre-dialytic stage, where exercise benefits appear to be greatest and most prolonged, allowing

significant improvements throughout the varying stages of the disease progression - functional capacity for ADLs (activities for daily life), aerobic capacity, muscle strength, blood pressure are all influenced without increasing the stress on renal function (Clyne 1991; Boyce 1997; Kouidi 2002). Fitts et al (1999) found that exercise coaching and counselling was more beneficial in pre-dialysis patients than for those in dialysis, suggesting that as people approach the dialysis stage of treatment a *pre-habilitation* intervention could maintain and aid recovery of physical capacity on cessation of dialysis management, although interventions shorter than 12-weeks in certain populations may be inconsequential (Heiwe et al 2001).

Resistance training in pre-dialysis patients has shown to reduce the effects of catabolism of a low-protein diet and uraemia by ameliorating muscle mass (hypertrophy of type 1 and 2 muscle fibres), strength, protein use and nutritional status (Castaneda et al 2001), resisting the decline into disability and allowing a continued higher health-related quality of life (Kouidi 2002). Heiwe et al (2001) showed with resistance training at 60% 1RM brought about an increase in quadriceps strength of 60% and 70% and dynamic muscular endurance of 53% and 79% in the CKD group and healthy controls respectively, allowing the authors to conclude that the skeletal muscle of CKD patients responds to resistance training in a similar way to healthy muscle.

A review of exercise interventions in CKD (Howden et al 2012) determined that introducing a programme of supervised resistance training to the non/pre-dialysis (NDD) population may improve muscle function and strength, mobility and walking distance, and reduce inflammation as the anabolic stimulus of resistance exercise training may reverse the catabolic state of CKD by decreasing chronic inflammation. In the catabolic state where muscle wasting is common, resistance training may prevent reduction in skeletal muscle mass and improve muscle mass and function.

2.9 Overview of the Literature and Thesis study aims.

- CKD is a progressive condition.
- The prevalence of CKD is increasing as the population ages.
- CKD is associated with uraemic sarcopaenia, muscular atrophy, and malnutrition as a result of protein-energy wasting.
- CKD patients have increasing risk for frailty as the disease progresses, thereby reducing health-related quality of life through greater dependence on family, medication, and the NHS.
- Renal replacement therapy (RRT) in the form of haemodialysis (HD), exacerbates some aspects of muscle wasting, an effect that is amplified in diabetic patients.

Thesis Aim 1 (Chapter 4):

Explore the effect of CKD stage on body composition, strength and function in different stages of CKD (early and late stage) using standard clinical and frailty outcome measures.

- Greater survival rates have been observed in late-stage CKD patients with higher body mass index. This counter-intuitive phenomenon has been termed “reverse epidemiology” or the “obesity paradox” and has been documented in particular in ESRD patients on HD.
- It is therefore vital not just to stop muscular wasting (protein energy wasting), but also reduce excessive, sudden, or unplanned fat loss.
- First, it must be possible to accurately monitor and assess wasting in these patients, and later to evaluate the effectiveness of counter-measure interventions.
- Therefore, valid and reliable tools to assess body composition are essential to observe, investigate, and maintain a protective level of fat and fat-free mass.
- Most CKD body composition research has utilized DEXA, CT, MRI, anthropometry (skinfolds, limb circumference, waist-to-hip ratio, etc), BIA, and BMI. Limitations are present for each (Table 2.5), ranging from the most expensive and time

consuming (gold standards - DEXA, CT, MRI), to those unable to differentiate between fat and fat-free mass (anthropometry and BMI).

- High-resolution ultrasonography has previously been used in other populations to measure regional body composition, and can differentiate between muscle, fat, and bone, as well as produce images of muscle architecture. However, the clinical utility of the method has not yet been established for people with CKD.

Thesis Aim 2 (Chapter 5):

Aim 2a: evaluate the validity of ultrasound compared to a gold standard measure (MRI) of body composition in CKD patients.

Aim 2b: establish the reproducibility of ultrasound measurement of regional body composition (muscle and fat depths), with a view to assessing its utility as a method of monitoring change in CKD patients.

- Anabolic interventions to improve body composition of CKD patients by promoting protein synthesis, and preventing protein catabolism should be introduced.
- These should be implemented as early in the disease trajectory as possible in order to
    1. delay the progression to a later stage of CKD and the need for dialysis, and
    2. allow patients to present in the best possible shape for dialysis (ie with limited atrophy and frailty characteristics).
- Examining the body composition of patients earlier in the disease process (pre-dialysis) has been done before using DEXA and/or BIA, but mainly using anthropometrics and skinfolds.
- Using ultrasound to assess regional body composition, muscle size and architecture in pre-dialysis patients may be important to establish the extent of wasting prior to the need for dialysis, with greater accuracy, and to increase our understanding of the links between architecture of the muscle and objective (strength and function) and patient-reported (health-related quality of life) outcomes.

Thesis Aim 3 (Chapter 6):

To explore, in pre-dialysis CKD patients, the relationship between ultrasound-derived estimates of regional body composition (muscle and fat depth, and muscle architecture), and routinely employed measures for the assessment of body composition, physical function, and uraemic state, at this point in the disease trajectory.

- Interventions in early-stage CKD should be focused on increasing lean body mass (protein) via anabolic interventions (such as increased/ improved nutrition or hormone therapy), without exposing patients to further co-morbidities often associated with increased adiposity (obesity; metabolic syndrome, CVD, diabetes).
- Exercise interventions have proved effective in other chronic illnesses at bringing about changes in body composition and physiology, though the focus has often been on aerobic (endurance) exercise.
- Recent investigations have demonstrated that aerobic (endurance) exercise, though having anti-catabolic effects, does not promote anabolism whereas resistance training brings about anti-catabolic changes and anabolism.
- Resistance (strength) training is an effective anabolic intervention to increase body mass without placing strain on the cardio-respiratory system, so can be performed by those with a chronic or critical illness.

Thesis Aim 4 (Chapter 7):

To evaluate the effects of frequency of a resistance training programme in patients with stage 3 CKD.

Sub-aims of RT intervention (Chapter 7):

- Measure and compare any change in muscle size or architecture brought about by the different frequencies (once or three times per week) of the RT programme.
- Assess and compare any change from the RT programme in strength and ADL-related function, as well as reported patient-uraemic symptoms.

CHAPTER 3 - General Methods

3.1 Overview of the Project

3.1.1 Study 1 [Chapter 4]

Using standard assessment tools frequently employed in both clinical and research groups, patients early in the CKD process (CKD3) were compared to late stage (CKD5/ ESRD/ dialysis dependent) patients by assessing their body composition, strength, and function.

3.1.2 Study 2 [Chapter 5]

Results from Study 1 highlighted that there was indeed a clinical and statistical difference between the two stages in each measure, with CKD5 being demonstrably weaker than the "healthier" CKD3 patients. However, the anthropometric tests and other techniques to assess body composition were unable to differentiate between lean tissue (protein/ muscle) and non-lean tissue (fat), thus it could not be determined at this stage whether there was a correlation or relationship between the notable loss of strength and function, and the atrophy of muscle (loss of muscle mass), or whether the weakness is due to other factors within the disease and treatment process.

Therefore a tool was needed that can measure muscle and fat separately, allowing for oedema or other inflammation as well as being time-efficient and financially viable for routine use. Ultrasound (US) was tested for reliability (for repeated measures) and validity against a gold standard (MRI) for assessing whole and regional body composition.

3.1.3 Study 3 [Chapter 6]

Using the validated and reliable Ultrasound (US) from Study 2, the relationship between US-derived indices of regional body composition (muscle and fat) and strength and function were explored in early stage CKD (CKD3) patients in order to assess whether functional and neuromuscular correlates of muscle mass and muscle architecture are correlated with patient-reported uraemic symptoms.

3.1.4 Study 4 [Chapter 7]

In Study 3 it was observed that there are strong correlations between the different measures of muscle mass and architecture, uraemic symptoms, and markers of strength and function, in early stage CKD (CKD3).

An exercise intervention programme was therefore implemented in early-stage (CKD3) patients, with the intention to develop muscle through resistance (strength) training and thereby assess the prime factors involved in bringing about the improvement (or at least impaired loss) of strength, function, and health-related quality of life (HRQoL) in these CKD patients.

3.2 Participant Recruitment

All participants were recruited from a single hospital outpatient unit.

Comparing strength and function *(Study 1)* and the different correlations between muscle size, strength and function *(Study 3)* between CKD3 and CKD5 – Patients were approached for inclusion if they had been diagnosed with CKD stage 3 (CKD3: 30 ≤ GFR ≤ 59 mL/min) or stage 5 (CKD5: GFR ≤ 15 mL/min).

Ultrasound Validity and Reliability *(Study 2)* - Twenty (18 male, 2 female) CKD5 patients undergoing continuous ambulatory peritoneal dialysis (CAPD) volunteered to participate in the study.

Resistance Training Intervention *(Study 4)* - Forty-five consecutively presenting CKD3 patients were approached, of which twenty-eight patients initially showed interest in participating and received information packs including participant information sheet, informed consent form, and investigator contact details. Twenty-two returned the informed consent and agreed to attend for pre-randomisation assessments. Twenty patients took part in the baseline assessments.

3.2.1 Inclusion and exclusion criteria

Participants in each study were included if they were 18-years of age or over, were independently mobile, were fluent in written and spoken English and were able to give consent. Patients were excluded if they had any diagnosis of unstable angina or amputation that would mean they were unable to fully participate in the programme.

Patients were included in the main intervention (resistance training) study if they had been diagnosed with Chronic Kidney Disease Stage 3 (moderately reduced kidney function), had not transferred to dialysis treatment, with a Glomerular Filtration Rate (GFR) in the range 30-59 (45-59, CKD3a; 30-44, CKD3b). Patients were excluded from the study if they had any known skin conditions or allergies which may be affected by either the Ultrasound conductive jelly or the adhesive connectors for the Bioelectrical Impedance Analyser.

3.2.2 Ethical approval

Ethical approval was obtained from the local NHS Ethical Advisory Committee and Internal University Ethics Committee.

3.2.3 Consent

When participants attended their initial appointment with the principle investigator they were given an opportunity to ask any further questions and were advised that they could withdraw from the study at any point. Participants then provided written informed consent. The completed consent form was kept by the researcher and a second copy by the participant.

3.3 Outcome measures

All outcome measures were taken by a single assessor (blinded to group allocation) highly experienced in ultrasonography, anthropometry, and measures of physical strength and function, in both a clinical and laboratory setting.

3.3.1 Body composition assessments

3.3.1.1 Body Mass Index (BMI) - Height and Weight

Participants were weighed and measured for height wearing light clothing and with no footwear. Body weight was measured to the nearest 0.1 kg on a GSE digital platform scale, model 350 (GSE Scale Systems, www.gse-inc.com). Height was measured to the nearest 0.5 cm using a wall-mounted stadiometer (model S100; Ayrton Corp); participants stood upright with arms hanging at their sides.

Body mass index (BMI) was calculated using [weight (kg)/height (metres)^2].

3.3.1.2 Subjective Global Assessment (SGA)

SGA combines self-report, clinical assessment, and simple bedside evaluation. Factors assessed include weight change over the past six months and two weeks, dietary intake, GI (gastro-intestinal) symptoms persisting over two-weeks,

functional capacity, subcutaneous tissue and muscle wasting, and oedema and ascites (fluid accumulation in the abdomen). Fluid shifts or ascites must be considered carefully when interpreting change in body weight.

The 7-point SGA is an expansion of the rating categories for nutrition status (original SGA had three ratings: A, B, and C), increasing the spectrum to a seven-point scale from 1 (severely malnourished) to 7 (well-nourished). Several studies have reported a reproducibility rate of 80% using SGA in the assessment of hospitalised patients (inter-observer reliability, Detsky et al 1987).

SGA was assessed using a standard form and scoring system by a registered health professional.

3.3.1.3 Anthropometric assessment - Limb circumferences (thigh and upper arm)

Limb circumferences were measured using a flexible tape-measure (to the nearest 0.1 cm) on the right side of the participant's body unless affected by disability or disease. All measures were taken with the participant standing and relaxed with as little tension in the measured limb as possible. The tape measure was held perpendicular to the bone where possible (i.e. not necessarily horizontal to the floor).

Measurements were taken twice and the mean was reported.

Mid-arm circumference (MAC) was assessed at the mid-point of the upper arm, determined from the length of the humerus (bone) from the greater tubercle of the humerus (shoulder joint) to the lateral epicondyle of the humerus (elbow joint) as found through gentle palpation of the relevant joints.

Mid-thigh circumference (MTC) was assessed at the mid-point of the femur (bone) as located through gentle manipulation and palpation of the greater trochanter (hip joint) and the lateral epicondyle of the femur (knee).

3.3.1.4 Bioelectrical Impedance Analysis (BIA)

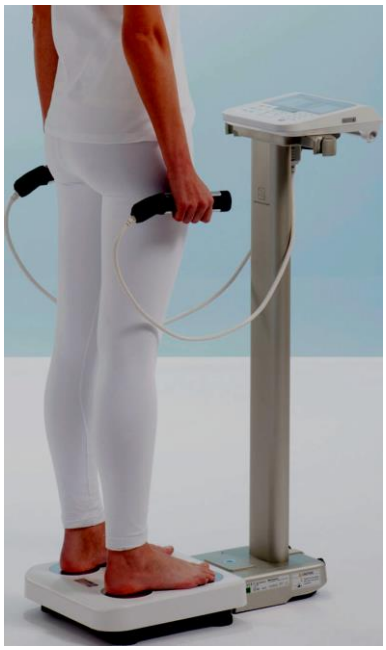
Whole body multi-segmental bioelectrical impedance spectroscopy/analysis was used to measure total body water, fat and fat free mass. Bioelectrical impedance analysis devices measure the change in impedance in body tissues by sending detectable electrical signals through the body. The method is based on the principle that fat-free mass (FFM) contains virtually all of the conducting electrolytes and water in the body which provide a good electrical pathway, whereas fat or fat-containing tissues produce a poor electrical pathway.

This has been validated in a number of populations, including healthy middle-aged (analysis against DEXA, segmental ICC 0.85-0.92, except truncal ICC 0.69, and whole-body ICC 0.88-100, Ling et al 2011; truncal ICC 0.94-0.99, appendicular ICC 0.63; Karelis et al 2013), the morbidly obese (against DEXA, truncal FFM ICC 0.788, appendicular FFM ICC 0.318-0.860, truncal FM ICC 0.643, appendicular FM ICC 0.287-0.558, Jimenez et al 2012) and athletes (against hydrostatic weighing and skinfolds, FFM ICC 0.96, Utter & Lambeth 2010), and has regularly been used in research where body composition assessment is necessary.

Measurements of whole and segmental body composition were taken using a Bioelectrical Impedance Analyser that could assess body composition in under one-minute (Tanita MC-780-MA multi-frequency segmental body composition analyser, Tanita Europe, Amsterdam). Participant height and weight were recorded, along with age, ethnicity (caucasian/non-caucasian), and body-type (athletic/standard).

Participants stood upright, with weight distributed evenly. Bare feet were placed on the sensitive metal foot-plate, and bare hands gripped the handles securely, with arms hanging loosely by their sides (Figure 3.1).

Figure 3.1 – BIA equipment in use



To ensure complete passage of the electrical current through the body, the investigator was careful to ensure no skin was touching at joints (such as thighs, or the upper arm touching the trunk); participants were encourage to wear comfortable (well-fitting) clothes, to hinder any potential short circuit which could give invalid readings.

3.3.1.5 Ultrasound (US) Imaging

All ultrasound measurements were performed with a brightness mode (B-mode), real time portable ultrasound system (SonoSite® 180 Plus, SonoSite Inc, Washington, USA) using a 50mm, 7.5MHz linear array probe. Participants lay supine for a period of 20 minutes prior to any measurements being taken to allow fluid shifts to occur (Berg et al, 1993). Compression of the tissues was kept to an

absolute minimum by using generous amounts of water-soluble transmission gel and maintaining a consistent low pressure with the ultrasound probe throughout scanning. Participants were instructed to relax the leg muscles during all measurements. All ultrasound measurements were performed on the right-hand side of the body.

3.3.1.5.1 Muscle and fat depth/thickness measurements

Muscle and fat thickness measurements were recorded in the axial plane along the mid-sagittal line of the VL at the mid-femur. Once the image was located, the screen was frozen and the system callipers were used to measure tissue thicknesses.

Figure 3.2a – Screenshot from Sonosite US at mid-VL in the axial plane (ID has been redacted)

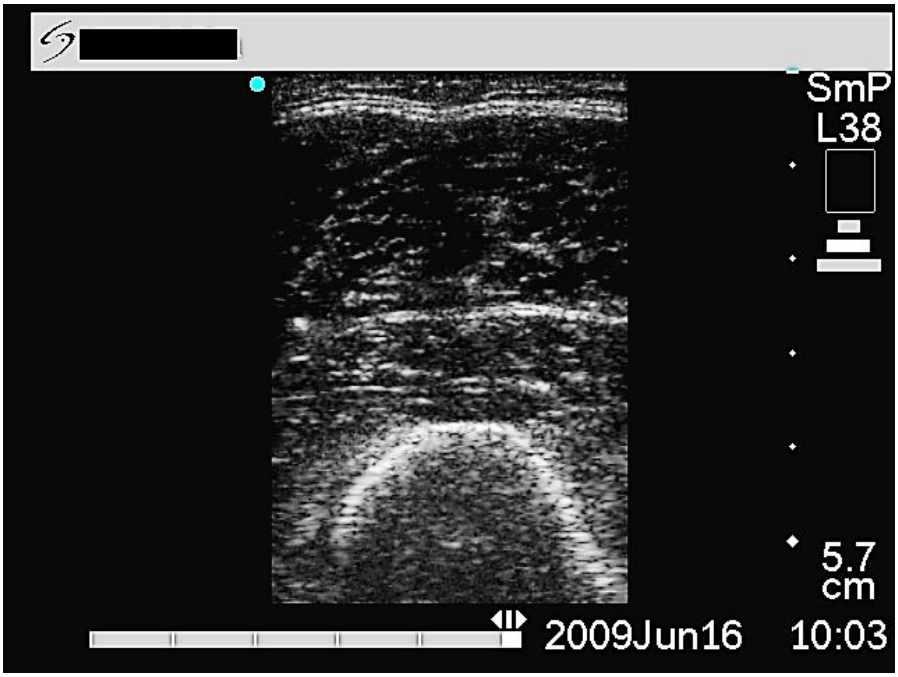
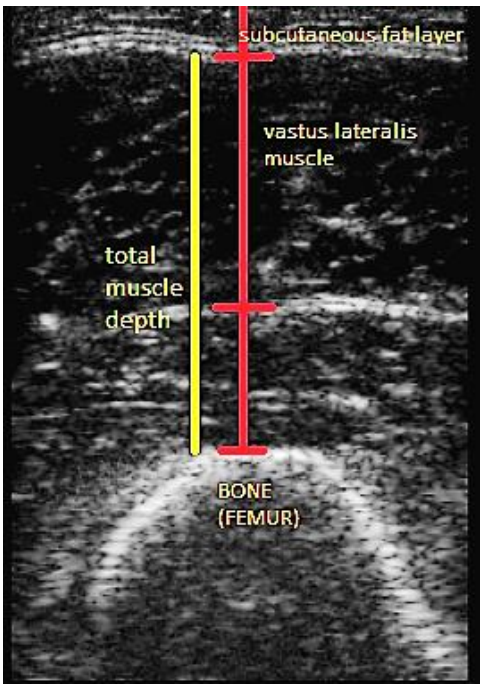


Figure 3.2b – Zoom of screenshot, showing the border between subcutaneous fat, VL and total muscle, and bone



Fat thickness was measured as the distance between the dermal surface and the fat - VL muscle interface. VL muscle thickness was measured as the distance between the fat - VL muscle interface and the VL muscle - vastus intermedialis (VI) interface, thus examining the VL muscle only. Total muscle thickness was measured as the distance between the fat - VL muscle interface and the VI muscle - bone interface (see Figure 3.2b – ultrasound image). The accuracy of thickness measurements using this ultrasound technique has been established previously on human cadavers (Miyatani et al 2000).

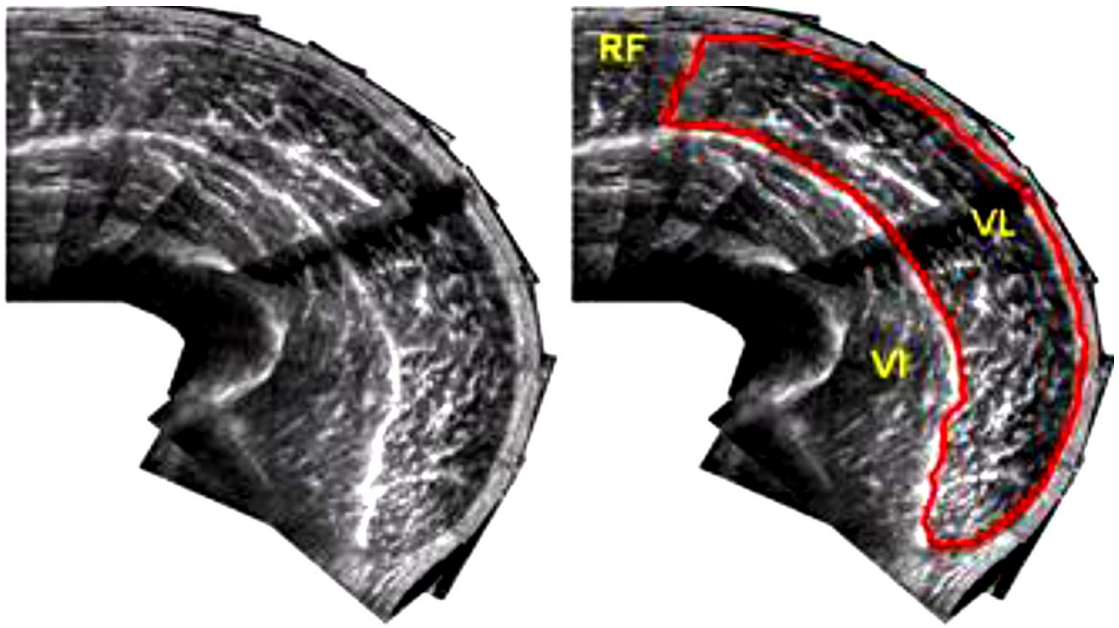
3.3.1.5.2 Anatomical cross sectional area (ACSA)

Anatomical cross sectional area (ACSA) of the vastus lateralis (VL) muscle was examined at mid-femur with the ultrasound probe held transversely, perpendicular to the dermal surface allowing a view of the muscle in the axial plane. Mid-femur was considered to be the distance halfway between the apex of the greater trochanter and the apex of the lateral epicondyle both of which were identified by

ultrasound. The probe was moved in a straight line from the lateral to the medial edge of the VL over echo-absorptive external markers that were placed on the skin.

All ultrasound scans were recorded onto VHS videotape and then acquired via frame-capture software (Adobe Premier v5.1, Adobe Systems). The external markers used cast acoustic shadows on each image that acted as reference points to allow later reconstruction of the ACSA image on computer (Figure 3.3). The reconstructed ACSA images were measured using image analysis software (NIH Image version 1.6, National Institute of Health, Bethesda, USA).

Figure 3.3 – Reconstructed VL ACSA at mid-femur length



3.3.1.5.3 Muscle architecture

Resting pennation angle and fascicle length of the VL muscle was measured using ultrasonography. Images were obtained along the mid-sagittal line of the VL at the mid-femur length (as described above).

Figure 3.4a – Screenshot from Sonosite US of mid-VL in the sagittal plane.

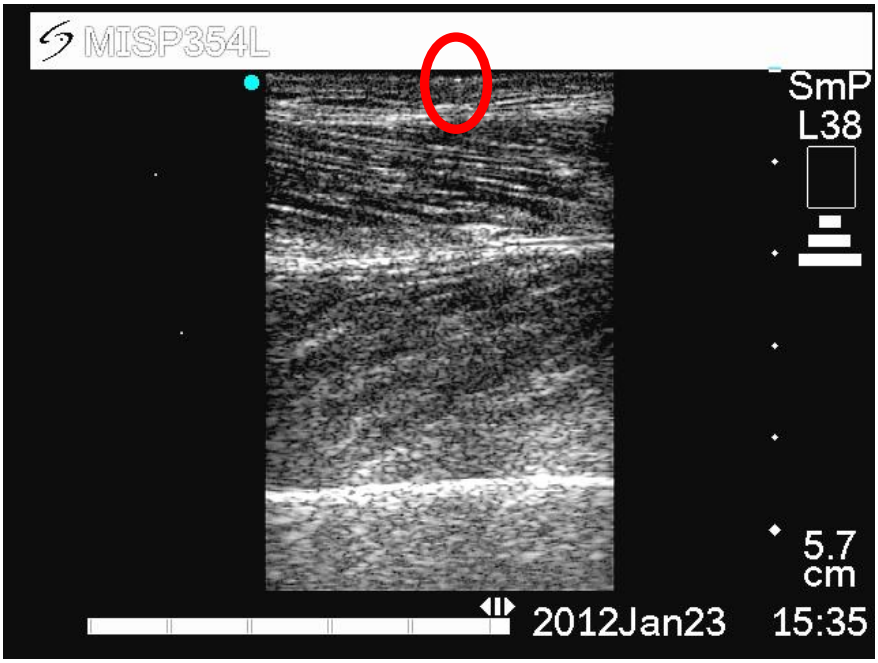
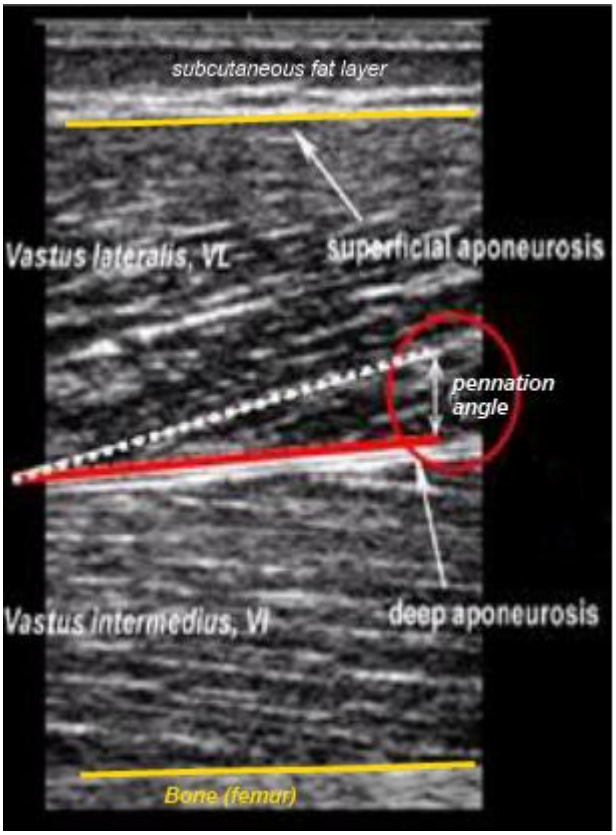


Figure 3.4a clearly shows the individual muscle fascicles (fibres) of the vastus lateralis, and the external marker shadow cast from the copper wire (the white dot, circled in red). Pennation angle was measured as the angle between the echoes of the deep aponeurosis and the echoes from the interspaces among fascicles (Fukunaga et al 1997).

Figure 3.4b – Zoomed in view of screenshot showing borders of fat, muscle, bone, and pennation angle of the muscle fibre



Fascicle length, defined as the length of the fascicle between the deep and superficial aponeurosis, was calculated using the following equation:

$$Fascicle\ length\ = \left[\frac{Mth}{\sin\theta}\right]$$

Mth = measured VL muscle thickness

θ = measured pennation angle (Abe et al 2001).

The ultrasound probe was positioned along the sagittal plane perpendicular to dermal surface to provide an image that included both the superficial and deep aponeurosis. Ultrasound scans were recorded on VHS videotape to enable subsequent analysis using the aforementioned image analysis software. The accuracy of ultrasound to assess the architecture of muscle has been previously

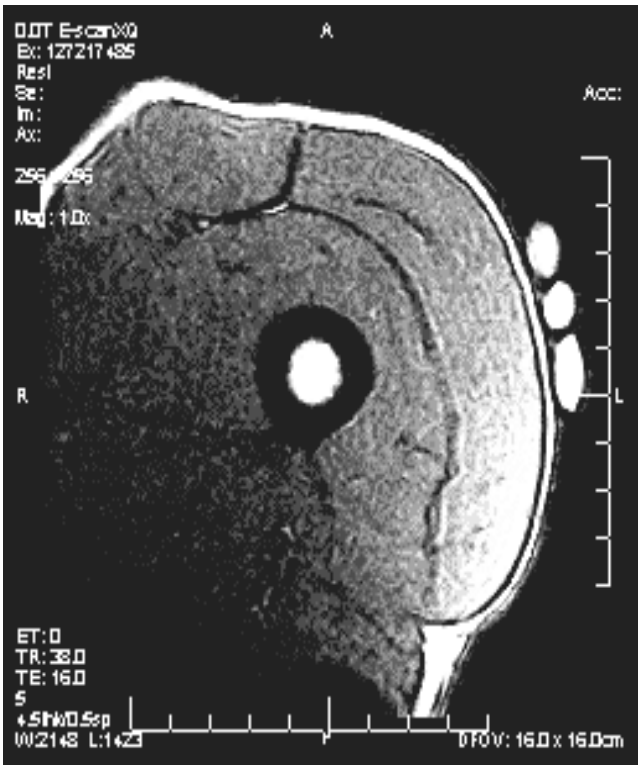
validated against direct anatomical inspection on cadavers (Kawakami et al 1993; Narici et al 1996).

3.3.1.6 Magnetic Resonance Imaging (MRI)

Using a 0.2T magnetic resonance imaging (MRI) extremities scanner (E-Scan, ESAOTE Biomedica, Genova, Italy) with a flexible coil, axial plane scans were obtained for the left leg of all participants at mid-femur length. Axial plane scans were acquired using a T1 weighted spin echo profile with the following parameters - time to echo: 16ms; repetition time: 38ms; field of view: 160 x 160mm.

All participants lay supine for 20 minutes prior to and during the scanning procedure.

Figure 3.5 - MRI scan of the VL at mid femur length.
Note the middle oil capsule denotes the mid-VL point as marked on the skin.



Oil capsules were placed lightly on the surface of the skin along the mid-femur length line to highlight this point precisely on the MRI scan; the oil capsules are clearly visible on T1 weighted MR images (Figure 3.5). The capsules were oriented in a manner such to allow the examiner to identify precisely the mid-VL point. ACSA of the VL muscle was determined at the mid femur length. VL muscle thickness and fat thickness were obtained at mid-VL (as described earlier) from the MRI scans. Images were analysed using digitizing software (NIH Image).

3.3.2 Functional tests

A standard warm-up was preformed prior to any exercise assessments (Functional and Strength), using an unloaded cycle ergometer for 5 minutes. Rest was taken as required throughout the assessments.

3.3.2.1 Sit-to-stand 5 (STS5) and sit-to-stand 60 (STS60)

Standing up from a seated position is a common and essential activity which enables other activities to take place. This is an important component to maintaining independence for the more frail population and has been validated as a measure of function by Goldberg et al (2012) in older (older females) and frailer populations (with balance disorders, Whitney et al 2005).

The STS tests were performed with a standard height chair (42cm) with no arm rests. To avoid aiding the movement (by raising the arms during the upward motion), the participants were asked to keep their hands on their waist or across the chest throughout the test (Bohannon 1995). The movement was first demonstrated by the assessor before being performed by the participant. The test was started with “3-2-1-Go!” whereon the participants would begin.

STS5: Time was recorded over the period needed to complete five sit-to-stand-to-sit movements. The movement was self-paced and allowed for as many rests as necessary.

STS60: A full count of "one" would be tallied once the participant had stood fully upright, and returned to the seat (sit-to-stand-to-sit). This procedure was repeated as many times as they were able in 60-seconds; self-paced, and allowing for as many rests as were necessary within the minute (Bohannon 1995).

3.3.2.2 North Staffordshire Royal Infirmary walk test (NSRI walk test)

The North Staffordshire Royal Infirmary walk test (NSRI walk test; Mercer et al 1998) involved a walk along a straight length of hospital corridor for 50-metres, followed by a stair-climb of 22 steps (3.3-metre elevation, individual step height 15cm) then immediately back to the start via descent of the same stairs, and 50-metre walk.

As described by Mercer et al (1998), participants were instructed that to complete the course they should "walk as quickly as possible" (Mercer et al 1998, p2024). The corridor and stairs were well-lit and with little traffic. Flooring was non-slip, and participants wore flat, comfortable shoes.

Total time and splits for each component were recorded using an electronic stopwatch by the assessor/investigator. Time was recorded and reported in seconds.

3.3.2.3 Seven-day Physical Activity Recall (PAR)

A standard questionnaire/interview was used to determine the level of activity performed by each participant over the previous seven days. The Seven-Day Physical Activity Recall (PAR) interview was originally developed for use in the

Stanford Five-City Project in the early 1980s (Sallis et al 1985). Because it is a general-purpose measure of physical activity that has been evaluated many times over the years it is widely used in epidemiologic, clinical, and behaviour-change studies.

The PAR is a semi-structured interview that estimates an individual's time spent in physical activity, strength, and flexibility activities for the seven days prior to the interview. The general interview format is as follows: an interviewer asks the participant to recall time spent sleeping and doing physical activities for the past seven days. The interviewer guides the participant through the recall process, day-by-day, to determine duration and intensity of the physical activities.

Although the PAR is designed to include a variety of physical activities, such as aerobic exercise, work-related activities, gardening, walking, recreation and leisure-time physical activities, only physical activities of moderate intensity and greater are counted. From hours spent in moderate, hard and very hard intensity physical activities, total kilocalories expended over the seven-days can be estimated.

3.3.3 Strength tests

A standard warm-up was preformed prior to any exercise assessments (Functional and Strength), using an unloaded cycle ergometer for 5 minutes. Rest was taken as required throughout the assessments. Each strength test was repeated for a total of three attempts, recording all but using only the best score for analysis. The movement was first demonstrated by the assessor before being performed by the participant. Each strength test was performed on the same side of the body as the body composition (muscle and fat depth) measures.

3.3.3.1 Handgrip dynamometry

A standard grip dynamometer (Lafayette Instrument, Lafayette, IN) with adjustable grip for hand size, was used. Participants stood with arms loosely by their sides, gripping the device in the suitable hand, thumb forward. Instructed not to lift their arm, bend their elbow, or raise their shoulders, participants squeezed the device as hard as possible and then relaxed (Chang et al 2011). The score was recorded and the device zeroed for the next attempt. The best of three attempts was used.

If unable to stand, participants were provided with the same seat that had been used for the functional tests, but were still instructed to have their arms straight and loose at the sides.

Hand-grip strength was measured using a dynamometer as a direct marker for upper body strength. It has also been shown to be an appropriate proxy marker for mobility (timed-up-and-go, $r=-0.59$, $p<0.0001$) and HRQoL (physical component of SF36, $r=0.38$, $p<0.01$, mental component of SF36, $r=0.32$, $p<0.01$) of hospital inpatients (Jakobsen et al 2010), and as an independent predictor of renal outcomes in non-dialysis CKD patients (Chang et al 2011), allowing handgrip strength measurement to be used as a reliable and inexpensive tool in clinical practice to assess the nutritional status of patients with NDD CKD (malnutrition-inflammation score, Amparo et al 2013).

3.3.3.2 Leg press and Knee extension peak isometric force @45degrees

Methods described by Gleeson et al (2002) were repeated for knee extension and leg press peak force with the three static maximal voluntary actions separated by a recovery period of 120-seconds (2-minutes). The participant was situated in an upright seated position on the dynamometer with the knee flexed passively to 45° (0° = full knee extension).

The lower leg was supported in position 0.1-metres proximal to the lateral malleolus by a rigid adjustable system. The latter system incorporated a load cell (RDP Electronics Ltd, Wolverhampton, UK: range 0–1000 N) interfaced to a voltage signal recording system that provided analogue-to-digital conversion of muscle force (Cambridge Electronic Design Ltd, UK: 1902 medically isolated programmable amplifier/filter [zero amplification; no filtering]; 1401 plus laboratory I/O interface [12-bit ADC; sampling at 4 kHz]) (Gleeson et al 2002).

Participants were seated with the angle between the back and seat of the dynamometer chair set at 120° and the angle between the chair and horizontal frame set at 10° to the horizontal. The axis of rotation of the dynamometer was aligned with the anatomical axis of the knee joint (Gleeson et al 2002).

To measure the knee extension isometric peak force (KE PF), the participants were instructed to push forward against the ankle strap in a "kick" motion. Care was taken to avoid lifting the leg during the movement, or pulling the foot backwards prior to the movement (avoid gaining momentum). Participants were instructed to aim to straighten their leg (although the foot and leg would not move).

For the leg press isometric peak force (LP PF), the participants were instructed to pull back and down against the ankle strap as if to bring the foot to their bottom.

3.3.4 Uraemic Symptoms

Uraemic symptoms affecting HRQoL were measured using the Leicester Uraemic Symptom Score (LUSS). LUSS is a five-point Likert scale that evaluates symptom number (LUSS 1), frequency (LUSS 2) and intrusiveness (LUSS 3) of a selection of eleven symptoms commonly associated with kidney problems (sleep disturbance, muscle spasm/stiffness, excessive tiredness, pain in joints/bones, loss of muscle strength/power, poor concentration/mental alertness, restless legs, impotence/lack of sex drive, shortness of breath, itching, and loss of appetite). It was developed

and validated for use in the dialysis population by Wright & Stein (1993) (Wright et al 1994) and is widely used to assess patients' perception of the severity of the illness.

LUSS1: The number of uraemic symptoms experienced by the individual. Score: 0-11.

LUSS2: The frequency of each symptom is rated on a scale ranging from 0 to 4 (0 = never, 4 = every day).

LUSS 3: The perceived intrusiveness of each symptom is rated on a scale ranging from 0 to 4 (0 = not at all intrusive, 4 = extremely intrusive)

Total score: The summative score is 0-99.

3.4 Main (Resistance training) Intervention

3.4.1 Initial 1-RM assessment

The one-repetition maximum (1-RM) method can be defined as the maximum amount of weight lifted just one time, using proper form during a standard weightlifting exercise (McArdle et al 2001). The initial estimate of the individual's 1-RM was made using an assessment of submaximal effort and the following equation for untrained individuals (submaximal 7 to 10-RM represents approximately 68% of the 1-RM score):

1-RM (kg) = 1.554 x (7 to 10-RM weight, kg) – 5.181 (Braith et al 1993)

The initial weight, believed to be close to the person's maximum lifting capacity, is selected, and then weight is progressively added in small increments (usually 1.0-5.0kg increments in a healthy population, so adjusted to 0.5-2.5kg increments in this population) until the person reaches their maximum lifting capacity; 1-RM. The rest interval during successive attempts was a minimum of one-minute to provide enough recovery time before lifting the next heavier load (McArdle et al 2001).

3.4.2 Resistance training programme

Each supervised training session started with of a short (five-minute) aerobic warm-up on a mechanically braked (unloaded) cycle ergometer. This was followed by the main training intervention:

A series of lower extremity exercises were performed using fixed weight machines (knee extension, leg press, calf raise, hamstring curl) and bodyweight-resisted exercises (lunges, squats) were performed (45 minutes).

Participants completed 3 sets of 8 repetitions at 80% of the individual's one repetition maximum (3x8reps @ 80% 1RM). The recovery period between sets was one-minute, with two-minutes between each different exercise.

The main (resistance training) part of the intervention session was followed by a short cool-down (identical to the aerobic warm-up: five-minutes on the unloaded cycle ergometer) and general stretching of the trained muscle groups.

Total session time was one-hour.

Progression/adaptation: 1-RM was amended as required (when an individual could surpass the prescribed dose of 3 sets of 8 repetitions). The results of the fortnightly measure of leg press and knee extension peak force were used as a guide for advancement and progression.

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CHAPTER 4 - Strength, Function, and Body composition of CKD patients at different stages of the disease trajectory (CKD3 vs CKD5)

4.1 Introduction

Muscle wasting is a common manifestation of Chronic Kidney Disease (CKD) and is a direct contributor to the development of weakness and frailty observed in this population (Delgado et al 2013; Fouque et al 2008; Ebner et al 2013; McIntyre et al 2006).

Frailty and weakness through the decrease in physical strength and function has clearly been seen in dialysis patients of all ages, with the rate of deterioration in ESRD much greater than in healthy age-matched controls (Painter 2005; Johansen et al 2007). The reduced function has also been observed in the pre-dialysis stage, though the great majority of studies have focussed on ESRD patients (already undergoing maintenance dialysis). Some studies have endeavoured to quantify markers of function in a "general pre-dialysis" population (Padilla et al 2008; Heiwe et al 2001) and more recently in the individual stages (CKD stages 2-5; Hiraki et al 2013) to determine the extent of the loss of strength and function, at what stage it is initiated, and when it becomes significantly life-affecting and life-limiting.

The link between muscle wasting and frailty allows assessment of the latter by markers of the former. Nutritional status encompasses protein-energy status, and atrophy of both lean and fat mass. Assessing nutritional status in CKD patients is important to monitor the extent of atrophy throughout the disease progression, to limit the resultant frailty where possible. Recommended and frequently used tools of assessment of nutritional status of late-stage CKD (dialysis dependent) include

regular (monthly, semi-annual, or annual) assessment of body weight, BMI, anthropometrics (mid-arm circumference, and skinfold thicknesses), body composition, clinical measures (serum albumin, creatinine, cholesterol, blood urea nitrogen), dietary interview and subjective global assessment (Kamimura et al 2005).

Function has been strongly linked to nutritional status (stratified by subjective global assessment score), often allowing simple objective measures to be used as markers for other more complex measures (handgrip strength strongly correlated to lean body mass measured by DEXA, anthropometry, and creatinine kinase; Heimburger et al 2000). Malnutrition has also been strongly associated with low body fat percentage (by DEXA), high serum c-reactive protein (inflammatory marker) and being female (Heimburger et al 2000). The suggestion that indices of physical function could be used as a proxy for nutritional state is therefore not unique, and utilising the proxy measure in times where the direct measure is not available or accessible is commonplace.

Reduced function is also strongly correlated with increased risk of death in CKD patients (Painter & Roshanravan 2013) and low serum albumin (hypo-albuminemia) has been previously identified as the most powerful predictor of death in ESRD patients (Lowrie 1994). However, a recent study of this widely-used biomarker of nutritional status, has found it to be less correlated with other measures of nutritional status than previously thought, as over-hydration and protein loss into the urine and dialysate reduce serum albumin concentrations (Gama-Axelsson et al 2012). Reduced function increases dependence, frailty and morbidity in the renal population (Kaysen & Eiserich 2003) so monitoring individual changes accurately and regularly is essential in ongoing treatment.

Presently, no single marker can be regarded as the model to assess nutritional status in CKD patients, as various other factors such as metabolic alterations and fluid overload are common (Fouque et al 2007).

4.1.1 Aims and hypotheses

The primary aim of this cross-sectional, comparative study was to quantify the difference between two distinct stages of the CKD trajectory (CKD3 early in the disease process and CKD5/ ESRD where dialysis has been initiated) using recommended assessment tools that are commonly employed and locally available in hospitals, clinics, and research.

It was hypothesized that patients in the final stage of CKD (CKD5/ ESRD) would present with significantly decreased muscle mass (measured anthropometrically and by SGA) and this would be associated with a decline in physical function, activity levels, and an increase in patient-reported uraemic symptoms.

4.2 Methods

4.2.1 Participants

All participants were recruited from a single hospital outpatient unit.

All participants were informed of the protocol and procedures to be used, and informed written consent was obtained from each, as approved by the appropriate local NHS Scientific Merit and Ethics Committee.

4.2.2 Assessments

4.2.2.1 Clinical and Physical Demographics

Body mass index (BMI) was calculated using [weight (kg)/height (metres)^2]. Body fat percentage was calculated using the BIA available within the hospital/ clinic.

As part of the usual care of each patient, a standard blood draw was performed by a trained phlebotomist/nurse and analysed for haemoglobin (Hb) and serum albumin levels.

4.2.2.2 Subjective Global Assessment (SGA)

SGA combines self-report, clinical assessment and simple bedside evaluation. Factors assessed include weight change over the past six months and two weeks, dietary intake, GI (gastro-intestinal) symptoms persisting over two-weeks, functional capacity, subcutaneous tissue and muscle wasting, and oedema and ascites. SGA was assessed by a registered health professional, using a standard form and scoring system.

4.2.2.3 Anthropometric assessment - Limb circumferences (thigh and upper arm)

Limb circumferences were measured using a flexible tape-measure (to the nearest 0.1cm) on the right side of the participant's body unless affected by disability or disease. The tape measure was held perpendicular to the bone where possible (i.e. not necessarily horizontal to the floor). All measures were taken with the participant standing and relaxed with as little tension in the measured limb as possible. Measurements were taken twice, and the mean was reported.

Mid-arm circumference (MAC) was assessed at the mid-point of the upper arm, determined from the length of the humerus (bone) from the greater tubercle of the

humerus (shoulder joint) to the lateral epicondyle of the humerus (elbow joint) as found through gentle palpation of the relevant joints.

Mid-thigh circumference (MTC) was assessed at the mid-point of the femur (bone) as located through gentle manipulation and palpation of the greater trochanter (hip joint) and the lateral epicondyle of the femur (knee).

4.2.2.4 Strength and Function

Muscle strength was assessed using a handgrip dynamometer (Lafayette Instrument, Lafayette, IN) and Knee Extension peak isometric force assessed at 45° (KE PF 45) (Gleeson et al 2002). Results were based on the best of three attempts.

Sit-to-stand 60 (STS60, number of complete sit-to-stand movements within 60 seconds) and sit-to-stand 5 (STS5, time taken to complete five sit-to-stand movements) were performed from a standard chair height of 0.42 metres.

4.2.2.5 Health-related Quality of Life (HRQoL)

Uraemic symptoms affecting HRQoL were measured using the Leicester Uraemic Symptom Score (LUSS). LUSS is a five-point Likert scale that evaluates symptom number (LUSS 1), frequency (LUSS 2) and intrusiveness (LUSS 3) of a selection of eleven symptoms commonly associated with kidney problems (sleep disturbance, muscle spasm/stiffness, excessive tiredness, pain in joints/bones, loss of muscle strength/power, poor concentration/mental alertness, restless legs, impotence/lack of sex drive, shortness of breath, itching, and loss of appetite).

Participants were also asked to recall their physical activity over the last week (Physical Activity Recall).

4.2.3 Statistics

Following normality checks of the data distribution, standard statistical methods were used for the calculation of mean and standard deviations where appropriate.

Independent samples t-tests were used to evaluate differences between the two groups. Significance (two-tailed) was accepted at $p<0.05$.

4.3 Results

All results are presented as mean ± standard deviation unless otherwise stated. Tables 4.1-4.4 show group demographics and differences. Tables 4.5-4.6 show the groups split by gender for the same outcome measures.

Table 4.1 - Participant characteristics

	CKD Stage 3 30 ≤ GFR ≤ 59 mL/min	CKD Stage 5 GFR ≤ 15 mL/min
Sample size *n* (M:F)	51 (28:23)	105 (70:35)
Age *(years)*	59.9 ± 13.9	56.6 ± 14.6
Height *(cm)*	165.2 ± 9.3	167.4 ± 13.9
Weight *(kg)*	77.3 ± 14.2	78.5 ± 16.7
BMI *(kg/m^2)*	28.1 ± 4.5	28.3 ± 6.1
Total body fat *(%)*	32.5 ± 9.0	30.0 ± 11.8
Time on dialysis *(months)*	NDD	35.0 ± 36.3
GFR *(mL/min)*	45.7 ± 7.0	On dialysis

Presented as mean ± standard deviation; BMI = body mass index; GFR – glomerular filtration rate; NDD = non dialysis dependent

There were no significant differences ($p>0.05$) in physical demographics between the two groups.

Table 4.2 – Clinical and physical measures routinely used to assess extent of malnutrition in CKD and other chronically and critically ill patients

	CKD Stage 3 *N (M:F)*	CKD Stage 5 *N (M:F)*	difference
Hb *(g/dL)*	13.7 ± 1.8 *50 (27:23)*	11.5 ± 1.3 *121 (80:41)*	(-) 2.2 **
Albumin *(g/L)*	41.8 ± 3.0 *50 (27:23)*	38.2 ± 4.3 *121 (80:41)*	(-) 3.6 **
SGA *(score)* *Max score = 7*	6.3 ± 0.9 *51 (28:23)*	5.9 ± 1.4 *29 (19:10)*	(-) 0.4
Mid-arm circumference MAC *(cm)*	33.8 ± 3.9 *51 (28:23)*	29.7 ± 3.8 *48 (32:16)*	(-) 4.1 **
Mid-thigh circumference MTC *(cm)*	52.5 ± 5.9 *51 (28:23)*	47.9 ± 5.1 *31 (21:10)*	(-) 4.6 **

*Presented as mean ± standard deviation; *denotes significance at the p<0.05 level, ** p<0.01. Numbers in italics show actual participant number for that outcome measure as N (M:F); (+) represents CKD5 > CKD3, (-) represents CKD5 < CKD3; Hb = haemoglobin; SGA = subjective global assessment, where 1=severely malnourished, 7=well-nourished*

Table 4.3 – Objective measures of muscular strength and endurance

	CKD Stage 3 *N (M:F)*	CKD Stage 5 *N (M:F)*	difference
Sit-to-stand 5 *(seconds)*	16.2 ± 10.7 *50 (27:23)*	13.0 ± 6.9 *115 (77:38)*	(-) 3.2 *
Sit-to-stand 60 *(count)*	21.9 ± 9.3 *48 (26:22)*	21.5 ± 7.5 *44 (31:13)*	(-) 0.4
Handgrip *(kg)*	27.4 ± 11.8 *50 (27:23)*	31.3 ± 10.0 *72 (48:24)*	(+) 3.9 *
Knee extension peak force KE PF 45 *(Newtons)*	303.7 ± 134.5 *39 (20:19)*	254.0 ± 72.0 *55 (39:16)*	(-) 49.7 *

*Presented as mean ± standard deviation; *denotes significance at the p<0.05 level, ** p<0.01. Numbers in italics show actual participant number for that outcome measure as N (M:F); (+) represents CKD5 > CKD3, (-) represents CKD5 < CKD3*

Table 4.4 – Patient reported activity and HRQoL (uraemic symptoms)

	CKD Stage 3 *N (M:F)*	CKD Stage 5 *N (M:F)*	difference
Physical Activity Recall *(kcal/kg/day)*	35.4 ± 2.8 *51 (28:23)*	34.9 ± 3.0 *30 (20:10)*	(-) 0.5
Complete seven-day PAR *(kcal/week)*	247.6 ± 19.9 *51 (28:23)*	157.0 ± 113.9 *30 (20:10)*	(-) 90.6 **
LUSS 1 *(number)* *Max score = 11*	5.9 ± 2.4 *51 (28:23)*	8.0 ± 2.3 *72 (47:25)*	(+) 2.1 **
LUSS 2 *(frequency)* *Max score = 44*	14.5 ± 7.4 *51 (28:23)*	20.5 ± 9.1 *72 (47:25)*	(+) 6.0 **
LUSS 3 *(intrusiveness)* *Max score = 44*	8.5 ± 6.4 *51 (28:23)*	15.9 ± 8.6 *72 (47:25)*	(+) 7.4 **

*Presented as mean ± standard deviation; *denotes significance at the p<0.05 level, ** p<0.01. Numbers in italics show actual participant number for that outcome measure as N (M:F); (+) represents CKD5 > CKD3, (-) represents CKD5 < CKD3*

Table 4.5 – Gender-specific participant physical characteristics

	CKD Stage 3			CKD Stage 5			Group difference (CKD3 v CKD5)	
	Male	Female	Gender difference	Male	Female	Gender difference	(+) = CKD5 > CKD3 (-) = CKD5 < CKD3	
N	28	23	(+) = M > F (-) = M < F	70	35	(+) = M > F (-) = M < F	Male	Female
Age *(years)*	59.8 ± 15.2	60.2 ± 12.4	(-) 0.3	58.9 ± 15.0	53.5 ± 13.3	(+) 5.4	(-) 0.9	(-) 6.7
Height *(cm)*	170.9 ± 7.6	158.3 ± 5.9	(+) 12.6 **	173.1 ± 7.4	156.4 ± 18.1	(+) 16.9 **	(+) 2.2	(-) 1.7
Weight *(kg)*	80.2 ± 15.0	73.8 ± 12.6	(+) 6.4	83.7 ± 16.4	73.4 ± 16.9	(+) 10.3 **	(+) 2.5	(-) 0.4
BMI *(kg/m^2)*	27.3 ± 3.9	29.1 ± 5.0	(-) 1.8	28.1 ± 5.2	29.3 ± 8.1	(-) 1.2	(+) 0.8	(+) 0.2
Body fat *(%)*	26.3 ± 5.7	40.0 ± 6.1	(-) 13.7 **	24.0 ± 8.4	43.5 ± 4.7	(-) 19.5 **	(-) 2.3	(+) 3.5
Time on dialysis *(months)*	NDD	NDD	0	23.2 ± 21.4	35.9 ± 39.7	(-) 12.7		
GFR *(mL/min)*	45.7 ± 8.5	45.7 ± 4.7	0	On dialysis	On dialysis	0		

*Presented as mean ± standard deviation; *denotes significance at the p<0.05 level, ** p<0.01; BMI = body mass index; GFR = glomerular filtration rate*

Table 4.6 – gender-specific group differences (clinical, strength, function, and uraemic symptoms)

	CKD Stage 3			CKD Stage 5			Group difference (CKD3 v CKD5)	
	Male	Female	Gender difference	Male	Female	Gender difference	(+) = CKD5 > CKD3 (-) = CKD5 < CKD3	
N (%)	55% [n]	45% [n]	(+) = M > F (-) = M < F	67% [n]	33% [n]	(+) = M > F (-) = M < F	Male	Female
Hb *(g/dL)*	14.8 ± 1.6 [27]	12.4 ± 1.2 [23]	(+) 2.4 **	11.5 ± 1.3 [80]	11.2 ± 1.2 [41]	(+) 0.3	(-) 2.2	(-) 1.2
Albumin *(g/L)*	41.9 ± 3.0 [27]	41.7 ± 3.0 [23]	(+) 0.2	38.3 ± 4.4 [80]	38.1 ± 3.8 [41]	(+) 0.2	(-) 3.5	(-) 3.7
SGA *(score)*	6.3 ± 1.1 [28]	6.2 ± 0.7 [23]	(+) 0.1	5.7 ± 1.6 [19]	6.8 ± 0.5 [10]	(-) 1.1	(-) 0.6	(+) 0.6
MAC *(cm)*	33.2 ± 3.8 [28]	34.4 ± 4.0 [23]	(-) 1.2	30.2 ± 4.7 [32]	29.6 ± 4.6 [16]	(+) 0.6	(-) 3.0	(-) 4.8
MTC *(cm)*	50.1 ± 5.2 [28]	55.5 ± 5.5 [23]	(-) 5.4 **	48.7 ± 6.9 [21]	47.9 ± 4.1 [10]	(+) 0.8	(-) 1.4	(-) 7.6
STS5 *(secs)*	12.8 ± 5.0 [27]	20.2 ± 14.2 [23]	(-) 7.4 *	11.8 ± 4.3 [77]	14.1 ± 7.4 [38]	(-) 2.3	(-) 1.0	(-) 6.1
STS60 *(count)*	24.6 ± 9.6 [26]	18.7 ± 8.1 [22]	(+) 5.9 *	23.8 ± 6.2 [31]	19.8 ± 8.5 [13]	(+) 4.0	(-) 0.8	(+) 1.1
Handgrip *(kgs)*	35.7 ± 9.5[27]	17.6 ± 3.8 [23]	(+) 18.1 **	35.9 ± 7.8 [48]	22.0 ± 7.0 [24]	(+) 13.9 **	(+) 0.2	(+) 4.4
KE PF 45 *(Newtons)*	382.6 ± 120.1 [20]	220.7 ± 93.7 [19]	(+) 161.9 **	285.4 ± 62.3 [39]	230.5 ± 54.4 [16]	(+) 54.9 **	(-) 97.2	(+) 9.8
PAR *(kcal/kg/day)*	35.8 ± 3.1 [28]	34.8 ± 2.5 [23]	(+) 1.0	35.1 ± 2.4 [20]	34.6 ± 4.0 [10]	(+) 0.5	(-) 0.7	(-) 0.2
LUSS1 *(number)*	5.5 ± 2.2 [28]	6.4 ± 2.5 [23]	(-) 0.9	7.6 ± 2.3 [47]	8.7 ± 2.2 [25]	(-) 1.1	(+) 2.1	(+) 2.3
LUSS2 *(frequency)*	12.7 ± 6.3 [28]	16.7 ± 8.1 [23]	(-) 4.0	18.5 ± 8.8 [47]	24.2 ± 8.6 [25]	(-) 5.7 *	(+) 5.8	(+) 7.5
LUSS3 *(intrusiveness)*	7.3 ± 6.0 [28]	9.9 ± 6.8 [23]	(-) 2.6	14.3 ± 8.3 [47]	18.9 ± 8.4 [25]	(-) 4.6 *	(+) 7.0	(+) 9.0

*Presented as mean ± standard deviation; *denotes significance at the p<0.05 level, ** p<0.01; [n] = actual participant number available for analysis; Hb = haemoglobin; SGA = subjective global assessment, where 1=severely malnourished, 7=well-nourished; MAC = mid-arm circumference; MTC = mid-thigh circumference; STS5 = sit-to-stand 5; STS60 = sit-to-stand 60; KEPF45 = knee extension peak force at 45 degrees; PAR = physical activity recall; LUSS = Leicester Uraemic Symptom Score*

4.4 Discussion

As hypothesized, the data showed statistical differences between the two groups, with the CKD5 (dialysis dependent) population performing worse in clinical (lower haemoglobin and plasma protein/albumin levels; Table 4.2), nutrition/body composition measures (smaller limb circumference; Table 4.2), strength (lower knee extensor maximal isometric force; Table 4.3), and HRQoL (increased burden, frequency, or intensity of uraemic symptoms; Table 4.4). Counter-intuitively, there were also significant differences in handgrip strength and STS5 (Table 4.3), with both of these measures showing CKD5 patients were stronger and faster.

However, there was no statistical difference in other objective measures of function (sit-to-stand 60; Table 4.3), or subjective global assessment (Table 4.2), body weight, body fat percentage, or BMI (Table 4.1). This was potentially due to an uneven gender split within groups (a greater proportion of male participants in the CKD5 group) and further exploratory analysis initially supported this theory (Tables 4.5 and 4.6).

4.4.1 Gender Difference

As expected, males were significantly taller with a lower percentage body fat than females (Table 4.5) and had statistically significant higher maximal handgrip and knee extensor (KEPF45) strength (Table 4.6) in both groups CKD3 and CKD5. Males were better performers in functional speed (STS5: faster/shorter time is superior) and endurance (STS60: higher count is superior) in both CKD3 and CKD5, but had no statistical advantage over the females in the CKD5 group (Table 4.6).

Despite handgrip strength being similar in both groups (though non-significantly higher in CKD5 for both genders; table 4.6), knee extensor strength was dramatically and significantly ($p<0.01$) different in males between CKD3 and CKD5.

Both genders were within the normal range for haemoglobin in the "healthier" (CKD3) group, though males had higher concentrations (Hb, $p<0.01$; Table 4.6) as is anticipated across a standard sample of males and females (although normal values for Hb in the general population differ by gender, this has not been addressed in most study designs of anaemia in CKD). However, males appear to again lose this advantage by stage 5 as the level of anaemia was very similar between genders and likely "stabilised" as patients below 11.5 g/dL are treated for anaemia according to the NICE guidelines on anaemia in CKD (NICE clinical guideline 114, 2011).

This would suggest that despite males performing statistically better than their female counterparts early in the disease process (CKD3) their advantage is largely lost by the point of receiving maintenance dialysis (CKD5) when both genders appear to be as weak and functionally limited as each other. This is also reflected in reverse; measures of mid-thigh circumference (MTC) revealed females having a greater thigh circumference in the healthier (CKD3) population than males ($p<0.01$) though it was significantly depleted by CKD5, reducing to levels below that of males in both stages CKD3 and CKD5 (MTC, Table 4.6).

The disproportionate number of females to males in one group (relatively even split in CKD3, but twice as many males as females in group CKD5; Table 4.1) may have skewed some of the data in one group. However, analyses comparing demographic data (height, weight, haemoglobin and percentage body fat) which are known to be affected by gender showed no overall group difference, so data could be pooled within each group.

4.4.2 Body composition and Markers of Malnutrition

There were no significant differences ($p>0.05$) between CKD3 and CKD5 patients in weight, BMI, percentage body fat (Table 4.1) and subjective global assessment (Table 4.2). However, the anthropometric measures (limb circumferences; Table 4.2) show highly significant ($p<0.01$) levels of wasting, also seen in the clinical results (Hb and Albumin, $p<0.01$; Table 4.2).

It has been well established that Hb levels fall as kidney function declines, as replicated in this study. Lower Hb levels have also been associated with increased cardiovascular abnormalities/events, increased hospitalisation, increased mortality, increased transfusion requirements and reduced health-related quality of life (O'Mara 2008). Haemoglobin is important for the transport of oxygen around the body and this reduced carrying-capacity could contribute to reduced energy levels and increased fatigue associated with advanced CKD.

Conversely, in this study there were no significant differences in serum albumin levels between genders or the different stages of the disease process despite serum albumin previously being used as a marker for malnutrition, strongly indicating that levels should theoretically be reduced as the disease stage worsens, with strong links between low serum albumin (hypo-albuminemia) and death in ESRD patients (Lowrie et al 1994). However, the results of this study do support previous research undertaken examining each stage (pre-dialysis CKD2-5), with serum albumin falling consistently (but not significantly) as CKD progresses (CKD3 4.18 ± 0.3 g/dL, CKD5 3.82 ± 0.4 g/dL, Table 4.2; CKD2 4.2 ± 0.3 g/dL, CKD3 4.0 ± 0.3 g/dL, CKD5 3.8 ± 0.3 g/dL, Hiraki et al 2013).

SGA (subjective global assessment) is by definition a subjective measure and hence open to a degree of error. It could be considered too broad a measure and unable to detect small changes in protein stores to truly assess nutritional status (or malnutrition). Research has suggested that SGA is only capable of discriminating between best and worst nourished patients, and has reported a large number of (haemodialysis) patients with strong evidence of significant malnutrition (determined by other clinical and physical measures) presented with a "normal" SGA score (Jones et al 2004), inferring that SGA is only truly sensitive enough to detect differences at a group level but certainly not for individual measures. The results of this study support the advice that SGA is not to be used alone but alongside other measures to determine the level of malnutrition (Cooper et al 2002; Kamimura et al 2005), including those used here (body weight and BMI, percentage body fat, and limb circumference) that describe a significant level of wasting by late-stage CKD.

4.4.3 Strength, Function, Activity, and Health-related Quality of Life

Isometric strength, measured by knee extensor ($p=0.02$) dynamometry, was significantly lower in the CKD5 group compared to CKD3. These results are consistent and in contrast with previous research where pre-dialysis patients (CKD2-3) have been compared to their equivalents in later-stages of CKD (CKD4) or already undergoing maintenance dialysis (CKD5/ESRD); CKD 2-3 were significantly better than CKD 4-5 in handgrip strength (different to present results) and knee extension(consistent with present results) (Hiraki et al 2013).

Functional measures examining speed (time taken to perform five sit-to-stand movements) were (unusually) significantly ($p<0.05$) slower in CKD3 than CKD5 (CKD3: 16.2 ± 10.9 seconds, CKD5: 13.0 ± 6.9 seconds, $p=0.03$), though the measure examining muscular endurance over one minute (STS60: the number of sit-to-stand

movements performed in sixty seconds), was not significantly different between groups (CKD3: 21.9 ± 9.3, CKD5: 21.5 ± 7.5, p=0.85).

The unaffected STS60 (functional muscular endurance) is counter-intuitive; decreased Hb (to the point of being categorised as anaemic) should affect performance as oxygen uptake capabilities are significantly reduced. Conversely, previous research has shown that even with stable Hb levels, function has been seen to decline in CKD patients, though that particular study used a group of patients further along in the disease trajectory (mix of CKD3-4 patients; Leikis et al 2006) than in the present analysis (mid-CKD3 in the pre-dialysis group only). Combining this information with that from Hiraki et al (2013) who demonstrated significant differences between CKD3 and CKD4 in strength assessments, we can infer that there may be a significant decline in STS60 (functional endurance) when patients progress to CKD4.

There were no differences between patient groups (or gender) in physical activity recall (PAR) which measures patient-reported activity levels over the previous seven days to calculate average energy expenditure per day. Low levels of physical activity and poor physical functioning are strongly associated with mortality and poor clinical outcomes in adult patients with CKD (Painter & Roshanravan 2013). The lack of variation in PAR between the two stages was unexpected as research and anecdotal evidence points to a reduced level of activity once patients are undergoing dialysis or even in late stage CKD5 before commencing/transferring to regular (maintenance) dialysis (Figure 2.1). When objectively measured (by accelerometer), physical activity has been found to be positively associated with GFR; greater (healthier) GFR with higher levels of physical activity (Hawkins et al 2011). However, this was not evident here, suggesting that patient physical activity recall is not sensitive enough to detect similar changes to those observed by

objective assessment, despite it being validated and deemed reliable in a series of studies.

Unsurprisingly, uraemic symptom number, frequency, and intrusiveness were significantly ($p<0.01$) more prevalent and problematic in CKD5 patients that CKD3 (Table 4.4).

4.4.4 Summary

The results of this study appear mixed with regards to the consistency with the current literature. The expectation and hypothesis was that individuals later in the disease process (CKD5) would fare worse than those earlier (CKD3) in all measures. However this was not seen to be the case in either handgrip strength (CKD5 were stronger) or STS5 (CKD5 performed faster).

Activities such as the endurance-based STS60 appeared unaffected by CKD stage, whilst lower-body strength (KEPF45) was significantly reduced in CKD5. Whether these last results are directly due to protein (muscle) wasting or other factors associated with later stages, such as actual treatment (dialysis), anaemia, nutrient loss or deficiencies from dialysis treatment or dietary changes, or reduced physical activity (though this was not observed here; PAR, Table 4.4) cannot be determined from the results of this study.

4.5 Study Limitations

The main limitation of this study is that it was a cross-sectional or “snapshot” study only and not longitudinal, so individual differences within each group were not controlled for. With a longitudinal study where participants were followed from

CKD3 to ESRD, data may be more robust and potentially demonstrate greater significance.

Other possible limitations did arise as not all measures were collected for all participants, once again affecting the statistical power as sample size numbers were distinctly smaller for certain measures in the CKD5 group (CKD5: SGA, n=13; MAC, MTC, STS60, n=18; PAR, n=30; KEPF, n=31). The male/female ratio remained constant, thus for these smaller sample sizes there were occasionally too few females to perform gender specific analyses between groups (CKD3 female compared to CKD5 females).

The disproportionate number of females to males in one group (relatively even split in CKD3, but twice as many males than females in group CKD5) may also be considered a limitation as it has potential to skew some of the data in one group. However, analyses comparing demographic data (height, weight, haemoglobin, and percentage body fat) which are known to be affected by gender showed no overall group difference, thus data could be pooled within each group.

4.6 Conclusions

There is a statistical difference between CKD3 (early stage, pre-dialysis) and CKD5 (end-stage, dialysis dependent) in some measures of strength, function, HRQoL (uraemic symptoms), and malnutrition, with CKD5 faring worse across a number of outcome measures.

It appears that SGA, BMI, body weight and percentage body fat are not precise enough assessment tools to distinguish between early-stage CKD (CKD3) and end-

stage (dialysis dependent) CKD (CKD5) at the individual level that is readily picked up by the anthropometric measures of limb size (mid-arm and mid-thigh circumference). The anthropometric measures used here were sensitive enough to detect the change between the groups (different disease stages). However, simple measures of limb circumference cannot differentiate and determine whether the observed atrophy is predominantly due to fat loss, lean tissue/protein/muscle loss, or an even proportion of both.

4.7 Implications for research

Regular monitoring of patients across the disease trajectory is vital to prevent excessive wasting and/or loss of function and to intervene appropriately and in a timely manner. This monitoring must be specific and accurate enough to be able to report individual changes in both regional and whole-body changes. Consequently, there is a need for a valid method of assessment of regional body composition that can distinguish between muscle and fat which is easily used, quick, accurate, reliable and sensitive to change.

CHAPTER 5 - The utility of high-resolution Ultrasound (US) imaging for the assessment of regional body composition in stage 5 chronic kidney disease patients undergoing continuous ambulatory peritoneal dialysis (CAPD CKD5)

5.1 Introduction

The prevalence of malnutrition and loss of muscle mass in end-stage renal disease (ESRD) can be an overwhelming complication of chronic uraemia (England & Price 1995). Malnutrition is consistently linked to increased mortality, morbidity and reduced health-related quality of life (HRQoL) in the dialysis (CKD5) population (Lowrie & Lew 1990) with muscle wasting recognized as one of the hallmark characteristics of renal disease (Kopple 1999). Malnutrition and reduced muscle mass have both been implicated in the functional decline of CKD patients (Brodin et al 2001; Fahal et al 1997) and in the ageing population (Russ et al 2012; Cesari et al 2009).

Skeletal muscle wasting in dialysis patients can be influenced by many individual factors (inactivity, sarcopaenia/ageing, medical treatment and comorbidities such as CVD, diabetes; Pupim et al 2005, peripheral vascular disease; Segura 2010), but is largely driven by the independent or interactive effects of malnutrition, disuse atrophy and a greater proportion of protein catabolism than protein synthesis (Workeneh & Mitch 2010). As the largest reservoir of protein within the body, skeletal muscle mass can serve as an excellent indicator of protein balance and hence may be clinically useful in assessing and monitoring the patient as the disease progresses.

In CKD stage 5 (CKD5) patients most body composition research (cross-sectional and interventional) to date has focused on patients undergoing haemodialysis (HD) with

peritoneal dialysis (PD) patient under-represented in the literature. This is partly due to the greater accessibility and availability of HD patients whilst dialyzing in hospital. Despite this, some comparative studies have been published that highlight the similarities and differences in the aetiology of wasting between the two principal CKD5 dialysis modalities (McIntyre et al 2006) and in some of the underlying muscle fibre characteristics (Sakkas et al 2004).

Patients treated with PD are often malnourished, presenting with low protein levels and decreased fat free (lean) mass (Vasselai et al 2008) but often with increased overall adiposity (greater visceral fat/subcutaneous fat ratio; Pellicano et al 2011). This may be partially attributed to the glucose-based dialysate used in PD as the increased availability of glucose in the dialysate promotes greater uptake and assimilation by the body (Schmidt & Salahudeen 1999), thereby potentially masking the extent of the underlying muscular atrophy. This may be unique in the dialysed population; however, a recent study (van Biesen et al 2013) used matched pair analysis to directly compare body composition and volume overload in HD and PD patients, finding no significant difference between the two groups though both had significantly less favourable results to a healthy reference population (reduced lean tissue mass and greater fat mass in both HD and PD populations than healthy; van Biesen et al 2013).

Additional factors contributing to the protein-energy malnutrition have been described elsewhere in a consensus statement for the International Society of Renal Nutrition (Carrero et al 2013; Figure 2.1) and include co-morbidities and interactions between metabolic acidosis, inflammation, endocrine/hormonal disorders, physical activity, drugs, genetic components and the effect of ageing.

Measures of speed, agility, and strength show peritoneal dialysis patients are less able in comparison to healthy age-matched controls, despite similar muscle mass (Brodin et al 2001). Hand-grip strength, as a surrogate marker for protein stores,

has been observed to be a good predictor of outcomes in dialysis patients (Wang et al 2005; Stenvinkel et al 2002). It is debatable whether the uraemia or the treatment itself is the main cause of this functional disability, or the summation of other factors including inflammation, but it remains the case that there is an underlying weakness that grows as the disease intensifies (Johansen et al 2007) and thus would benefit from being routinely monitored.

Anthropometric measures such as skinfold thicknesses and waist and limb circumferences are routinely taken with the intention of monitoring the nutritional status of CKD patients. However, basic measures such as limb circumference do not allow accurate composition analysis of the limb being measured (Roubenoff & Hughes 2000) and skinfold measures using calipers are highly prone to error - no matter how well trained and experienced the technician - as skin calipers have been shown to overestimate the subcutaneous fat thicknesses of the thigh in individuals with higher fat values (Selkow et al 2011).

The accurate measurement of muscle mass is therefore an important research and clinical tool for assessing change from an intervention, monitoring progression/deterioration associated with this stage of CKD or from disuse and frailty-related ageing. Direct measurement of muscle mass is not always feasible by means of Magnetic Resonance Imaging (MRI) or other reference methods (e.g. total body potassium or DEXA) due to financial or time costs, general patient access, or the sheer volume of patients that need to be monitored.

High resolution ultrasound (US) has shown great potential as an alternative (near-bedside/patient) method to assess muscle and fat mass at specific anatomical sites; it has been shown to accurately measure change in muscle size resulting from anabolic interventions and also to monitor the effects of ageing and disuse in a variety of populations though most were healthy and of working age (knee-joint injury, Uremović et al 2004; healthy men, Miyatani et al 2002; Miyatani et al 2004;

healthy adults and patients with multiple organ failure, Campbell et al 1995; older men and women, Bemben 2002; critically ill hemiplegic, Moukas 2002; working age healthy, Sanada et al 2006; healthy adults, Ahtiainen et al 2010).

Ultrasound is a relatively expedient method of this type of data acquisition and has been shown to safely produce high quality images of muscle size and structure (Table 2.3). Equipment is inexpensive in comparison to other clinical methods such as MRI or DEXA and can be taken to the patient at their bedside, in a research laboratory or other non-clinical site.

A recent literature review (English et al 2012a) indicated that there was good reliability (intra and inter-rater, same day and separate day test-retest reliability, all described as "generally high" with intra-class correlations greater than 0.7, coefficient of variations were "low" between 1.2-7.4%) for measuring muscle size across a number of limb sites in healthy populations. However, there is currently very limited evidence for the reliability of ultrasound to measure muscle size in clinical populations in general and none in CKD patients (English et al 2012a).

The purpose of this study was to examine the validity, reliability (reproducibility and potential sensitivity) and clinical utility of a US method compared to MRI for the assessment of quadriceps muscle (vastus lateralis, VL) anatomical cross-sectional area (ACSA), muscle thickness, and fat thickness in stage 5 CKD patients undergoing continuous ambulatory peritoneal dialysis therapy.

5.2 Methods

5.2.1 Participants

Twenty (18 male, 2 female) stage 5 CKD patients undergoing continuous ambulatory peritoneal dialysis (CAPD) for an average of 30.7 ± 32.2 months volunteered to participate in this cross-sectional study (Table 5.1).

All participants were recruited from a single hospital dialysis unit.

Table 5.1 - Participant/subject characteristics (n = 20, 18M, 2F)

Age (*years*)	56.5 ± 16.7 (median 60, range 17-79)
Height (*cm*)	170.1 ± 7.4
Mass (*kg*)	78.0 ± 15.4
BMI (*kg/m^2*)	26.8 ± 3.8 (median 26.3, range 19.9-38.7)
PD dialysis vintage (*months*)	30.7 ± 32.2

Presented as mean ± standard deviationunless otherwise stated; BMI = body mass index; PD = peritoneal dialysis

All participants were informed of the protocol and procedures to be used, and informed written consent was obtained from each, as approved by the appropriate local NHS Scientific Merit and Ethics Committee. Participants attended two sessions, seven days apart.

Ultrasound assessments were performed in both sessions at a similar time of day, and MRI measurements were made during the second visit only. US and MRI measurements were acquired in a counter-balanced fashion. All data was acquired with dialysate in the peritoneal cavity.

Strength data was obtained in the second laboratory session after completion of all US and MRI assessments.

5.2.2 Measurements

All ultrasound measures were taken by a single assessor, highly experienced in ultrasonography in both a clinical and laboratory setting.

5.2.2.1 Ultrasound (US)

All US measurements were attained in brightness mode (B-mode) via a portable ultrasound system (SonoSite® 180 Plus, SonoSite Inc., Bothell, Washington, USA) using a 7.5MHz linear array probe. Participants lay supine for a period of 20 minutes prior to any measurements being taken to allow fluid equilibration to occur (Berg et al 1993). The probe head was coated with water-soluble transmission gel which provided acoustic contact without depressing the dermal surface (Miyatani et al 2002). Compression of the tissues was kept to an absolute minimum by maintaining a consistent low pressure with the US probe throughout scanning.

All assessments were undertaken after identification of the measurement sites by palpitation and then US scanning of the key anatomical landmarks. The skin surface was marked with a non-permanent marker and an angioma (mole) map was constructed for each participant to ensure the correct location and placement of the probe for repeat assessments.

5.2.2.1.1 Anatomical Cross Sectional Area (ACSA)

ACSA of the vastus lateralis (VL) was examined by US at mid-femur (identified as the distance half way between the apex of the greater trochanter and the apex of the lateral epicondyle) with the ultrasound probe held transversely, perpendicular to the skin, thus allowing a view of the muscle in the axial plane. The probe was moved in a straight line from the lateral to the medial edge of the VL over external markers that were placed on the skin. All scans were captured on video-tape to allow subsequent analysis.

The external markers cast an acoustic shadow on each image which acted as reference points allowing the ACSA image to be reconstructed on a computer using imaging software (Adobe Photoshop, Adobe Systems Inc., California, USA). These reconstructed ACSA images were then measured using digitizing software (NIH image, National Institute of Health, Bethesda, Maryland, USA).

5.2.2.1.2 Depth or Thickness measurements

US muscle and fat thickness measurements were recorded in the axial plane at the mid-femur length/mid-VL width intersect (defined as mid-VL). Once the image was located the screen was frozen and the systems calipers were used to measure tissue thicknesses. Calipers were removed to capture a second image for later analysis.

Fat thickness was measured as the distance between the skin surface and the fat/VL interface (or tissue plane). VL muscle thickness was measured as the distance from the fat/VL tissue plane to the VL/VI tissue plane. All ultrasound measurements were performed on the left leg and were repeated after seven days.

5.2.2.2. Magnetic Resonance Imaging (MRI)

A 0.2T magnetic resonance imaging (MRI) extremities scanner (E-Scan, ESAOTE Biomedica, Genova, Italy) with a flexible coil was used to obtain axial plane scans at mid femur length for the left leg of all participants.

Axial plane scans were acquired using a T1 weighted spin echo profile with the following parameters - time to echo: 16ms; repetition time: 38ms; field of view: 160 x 160mm. All participants lay supine for 20 minutes prior to and during the scanning procedure. Oil capsules were placed lightly on the surface of the skin along the mid-femur length line to highlight this point precisely on the MRI scan; the oil capsules are clearly visible on T1 weighted MR images. The capsules were oriented in a manner such to allow the examiner to identify precisely the mid-VL point. ACSA of the VL muscle was determined at the mid femur length. VL muscle

thickness and fat thickness were obtained at mid-VL (as described above) from the MRI scans. Images were subsequently analyzed using digitizing software (NIH Image J).

5.2.2.3. Strength and function assessments

Participants performed a short aerobic warm-up using a cycle ergometer for five minutes prior to the strength assessments. Rest was taken as required throughout assessments.

Peak force (PF) during knee extension (KE) exercise at a joint angle of 45 degrees was measured on the dominant leg using an isometric dynamometer (described first by Gleeson et al 2002, and in Chapter 3, above). Participants practiced a few times to standardize the "kicking" motion. The best of three maximal knee extensions was then recorded, with a two minute rest between each attempt.

Sit-to-stand 60 (STS60) was measured as described in Chapter 3 (Methods). A full count of "one" was tallied once the participant had stood fully upright, and returned to the seat (sit-to-stand-to-sit). This procedure was repeated as many times as they were able in 60-seconds; self-paced, and allowing for as many rests as were necessary within the minute.

5.2.3 Statistics

Following normality checks of the data distribution, standard statistical methods were used for the calculation of mean and standard deviations where appropriate. Validity assessments (US measures and MRI) were determined by ICC, using a two-way random effects model (absolute agreement definition) (Rankin & Stokes 1998). Intra-observer reliability/repeatability for US measurement of the VL muscle, muscle thickness and ACSA was tested with an intra-class correlation coefficient (ICC) using a one-way random effects model (Shrout & Fleiss 1979).

Typical error (standard error of the measurement, SEM) was assessed for both intra-observer reliability of the ultrasound method, and as validity between US and MRI. SEM was calculated using the equation $SD_{diff}/\sqrt{2}$, where SD_{diff} is the standard deviation of the difference scores between the two tests. The minimally detectable change (MDC) of the US and MRI methods were defined using a 95% confidence interval and the equation $(1.96)(\sqrt{2})(SEM)$, (Weir 2005). Relationships between measures of muscle mass and muscle strength were assessed using Pearson's correlation coefficient.

Significance was set at $p<0.05$.

5.3 Results

All results are presented as *mean ± SD* and to two decimal places (2dp) unless otherwise stated.

5.3.1 Validity of US measurements

Ultrasound and MRI were highly and significantly correlated (ICC for ACSA 0.953, 95%CI [0.885, 0.982], p=0.000, VL muscle thickness 0.988, 95%CI [0.970, 0.995], p=0.000, and fat thickness 0.978, 95%CI [0.912, 0.994], p=0.000, Table 5.2) with no significant difference between the two methods ($p>0.2$ for all measures).

This was initially graphed with the line of equality between methods to demonstrate the correlation (figs 5.1a-c), before further assessing the limits of agreement using the Bland-Altman (1986) method. The line of equality represents perfect agreement between the methods (where x=y). Any data-points away from this line demonstrate a bias or level of disagreement.

Figure 5.1a - Comparison of MRI and US measures of VL ACSA

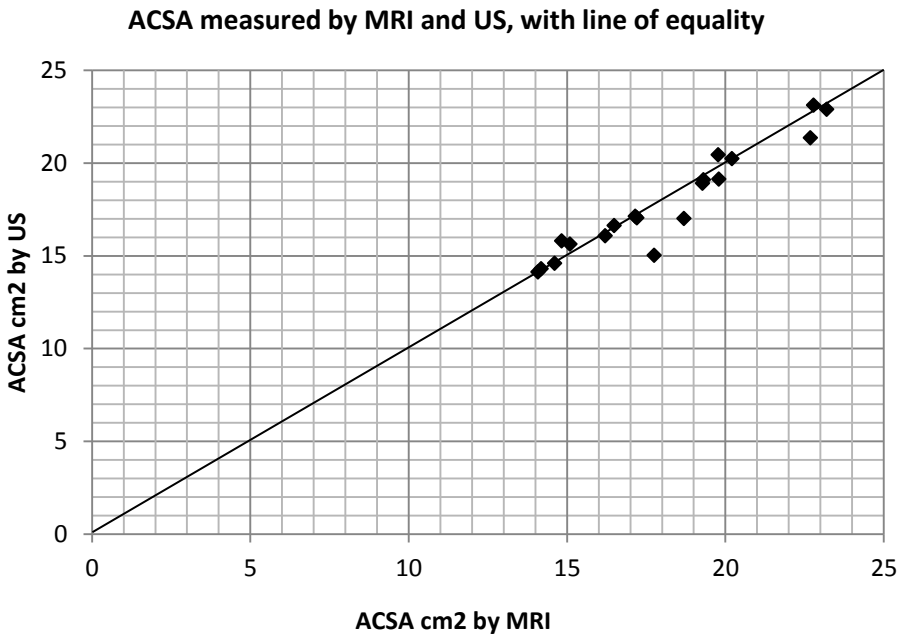


Figure 5.1b - Comparison of MRI and US measures of VL thickness

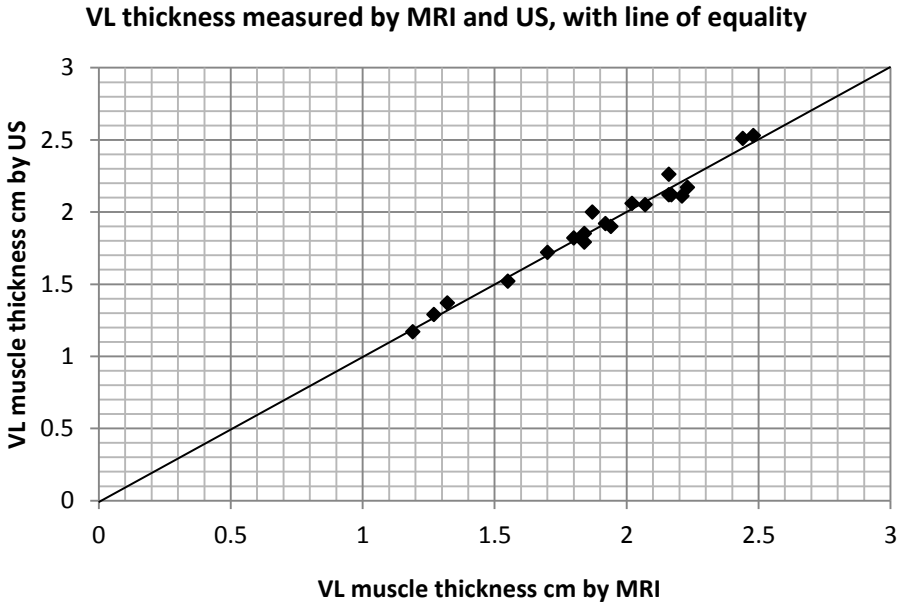


Figure 5.1c - Comparison of MRI and US measures of fat thickness.

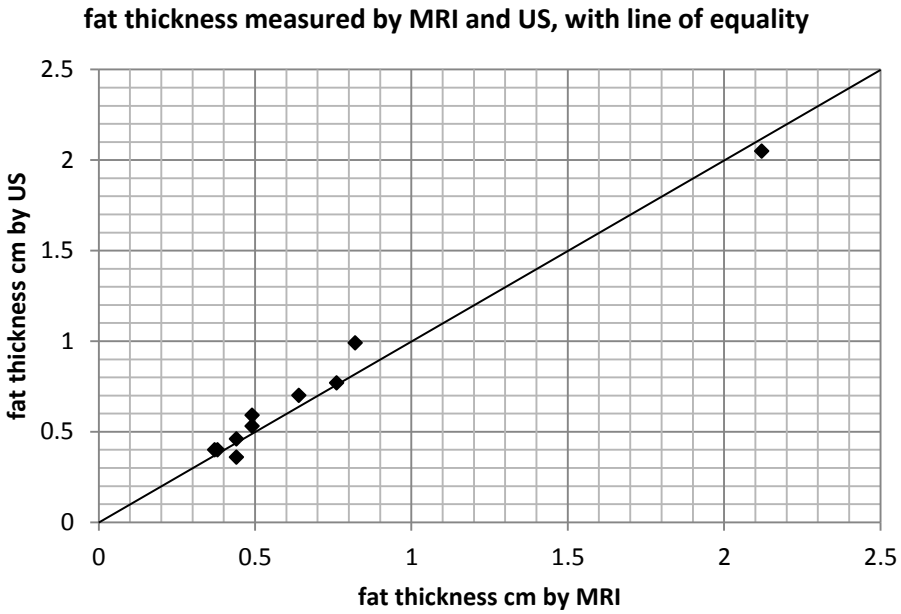


Table 5.2 summarizes the validity of Ultrasound measurement of the vastus lateralis (VL) muscle ACSA, muscle thickness, and subcutaneous fat compared to MRI measures.

Table 5.2 – US validity at mid-VL site compared to MRI (to two decimal places)

	N	US	MRI	ICC (95% CI)	Absolute difference	Typical error (95% CI)	Limits of Agreement
ACSA (cm^2)	19	17.82 ± 2.82	18.07 ± 2.92	0.95 (0.88, 0.98)	0.25 ± 0.86	0.61 (0.46, 0.90)	1.81
VL thickness (*cm*)	20	1.91 ± 0.37	1.91 ± 0.36	0.99 (0.97, 0.99)	0.00 ± 0.06	0.04 (0.03, 0.06)	0.12
Fat thickness (*cm*)	10	0.75 ± 0.60	0.70 ± 0.52	0.98 (0.91, 0.99)	0.03 ± 0.07	0.05 (0.04, 0.09)	0.17

Presented as mean ± standard deviation; ACSA = anatomical cross-sectional area; VL = vastus lateralis; ICC = intra-class correlation; US = ultrasound; MRI = magnetic resonance imaging

The mean (average) differences between ultrasound and MRI for ACSA (0.25 ± 0.86 cm^2) and VL thickness (0.00 ± 0.06 cm) show MRI yielding slightly higher values than US for each muscle index, with fat thicknesses marginally lower (-0.03 ± 0.07 cm).

Bland-Altman (1986) analyses were then performed and graphed (Figures 5.2a-c) of the two methods being compared (MRI and US) to illustrate the agreement between them, with the average of two methods along the (horizontal) x-axis (MRI*US/2) and difference of methods (MRI-US) on the (vertical) y-axis. Limits of agreement (1.96*SD) are shown with the dashed line and mean (absolute difference) by the solid line.

Figure 5.2a – VL ACSA Bland-Altman graph; average of two methods along the x-axis, and difference of methods on the y-axis

Limits of agreement (1.96*SD) are shown with the dashed line, and mean (absolute difference) by the solid line.

mean: 0.25 cm2, +1.94, -1.45

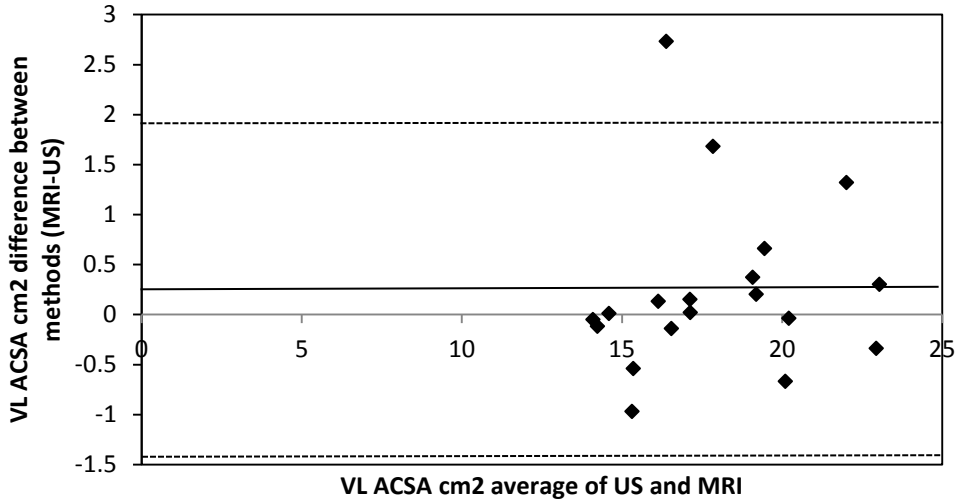


Figure 5.2b – VL muscle thickness Bland-Altman graph

mean: 0.00 cm, + 0.11, -0.12

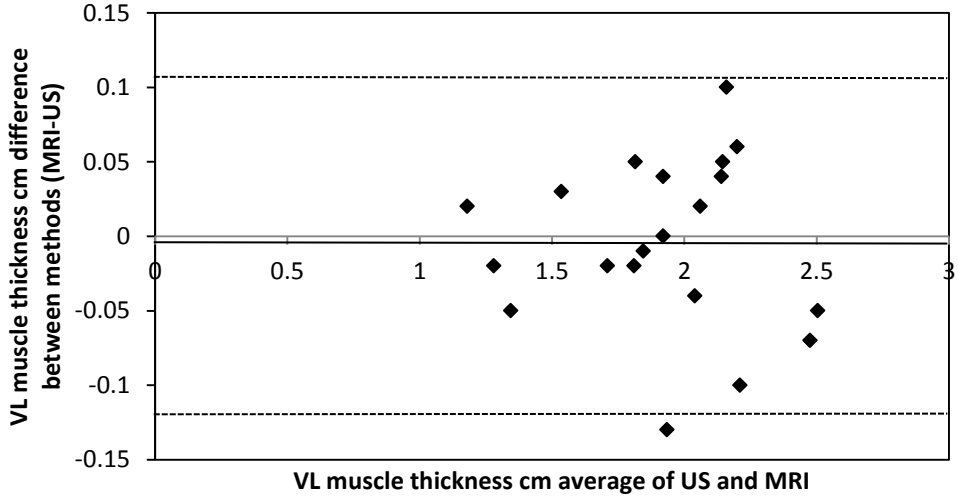
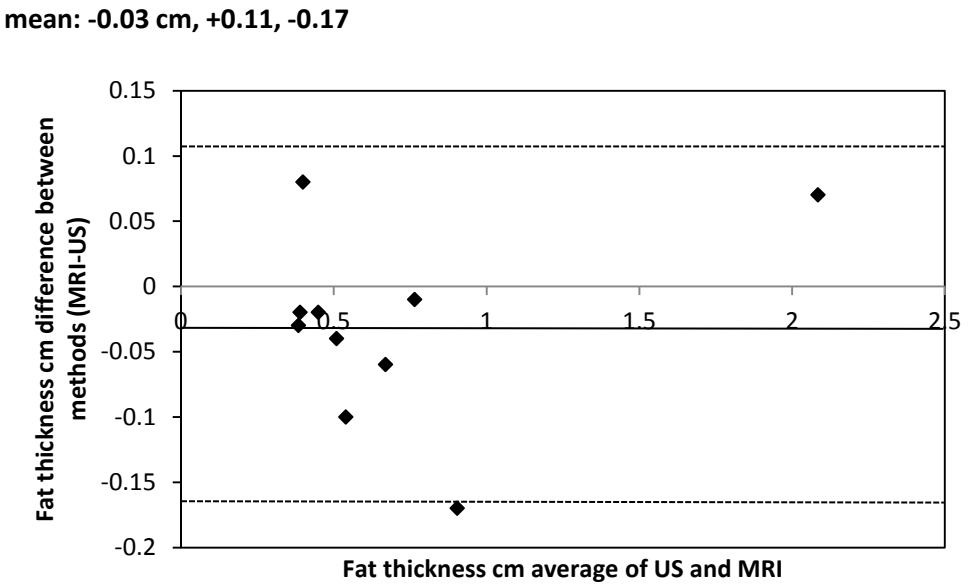


Figure 5.2c – Fat thickness Bland-Altman graph; average of two methods along the x-axis, and difference of methods on the y-axis

Limits of agreement (1.96*SD) are shown with the dashed line, and mean (absolute difference) by the solid line.



The sample size was too small to comment on whether accuracy changes with tissue size, and despite the limits of agreement being quite narrow; they may still have been affected by the one or two outliers.

Therefore, logarithmic transformations were performed to remove any skew, and further investigate any linearity and correlations. The modulus of the previously calculated average and difference were used in the log-transformation, and the new data was plotted (Figures 5.3a-c); $\log_{average}$ along the x-axis and $\log_{|difference|}$ on the y-axis. Limits of agreement (1.96*SD) are shown with the dashed line, and mean by the solid line.

Figure 5.3a – VL ACSA log-transformed Bland-Altman graph; $\log_{average}$ along the x-axis, and $\log_{|difference|}$ on the y-axis.

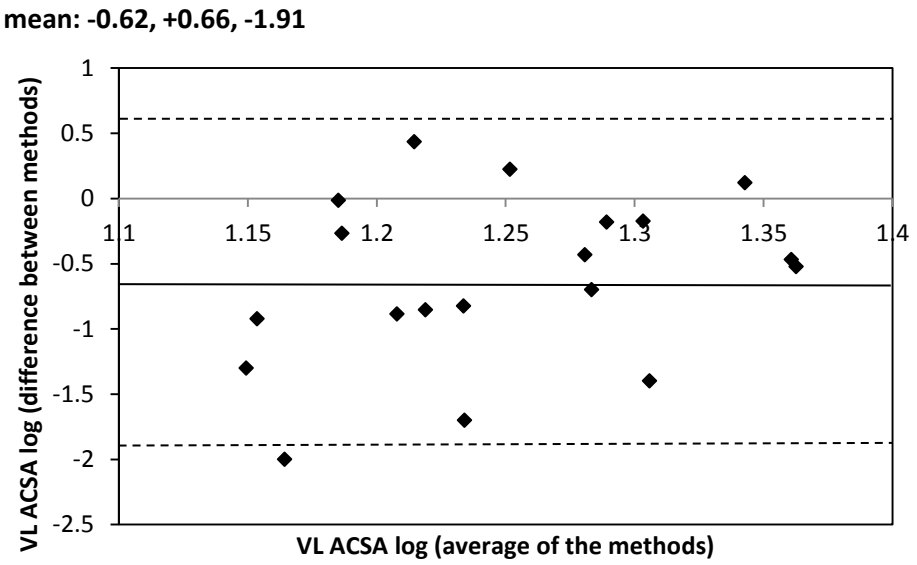


Figure 5.3b – VL log-transformed Bland-Altman graph; $\log_{average}$ along the x-axis, and $\log_{|difference|}$ on the y-axis.

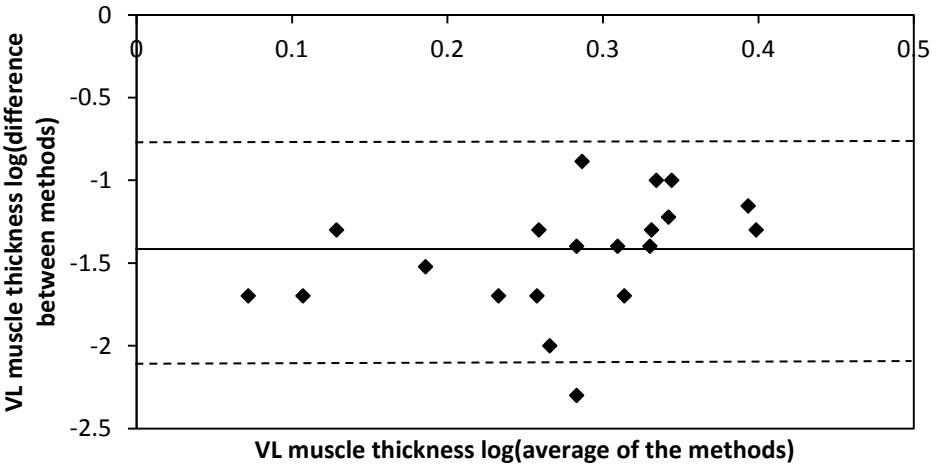
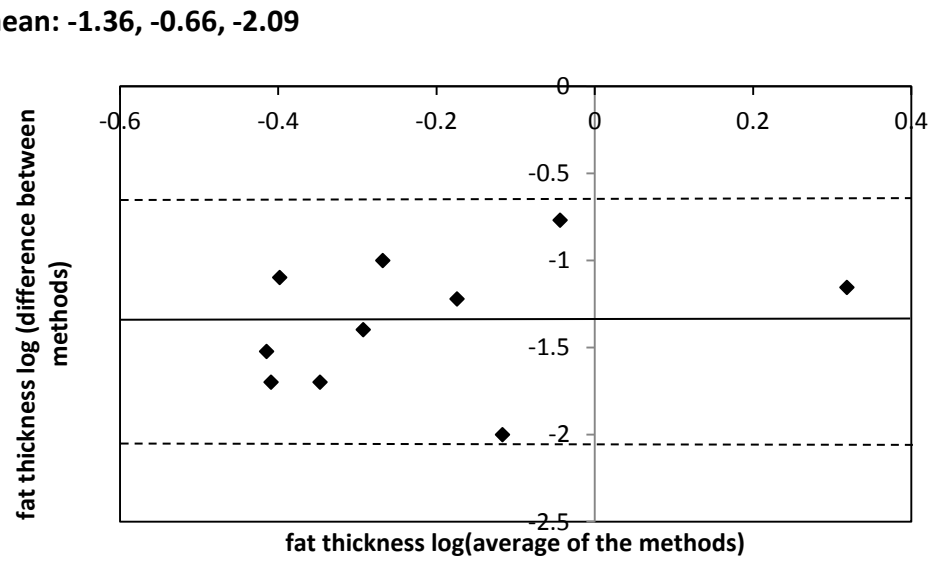


Figure 5.3c – Fat thickness log-transformed Bland-Altman graph; $\log_{average}$ along the x-axis, and $\log_{|difference|}$ on the y-axis.



5.3.2 Intra-rater reliability/repeatability of Ultrasound

The two consecutive sets of ultrasound measures (taken seven days apart) were highly correlated in the direct measures taken at the mid VL site; VL muscle thickness (ICC 0.981, 95%CI [0.953, 0.992], p=0.000) and fat thickness (ICC 0.992, 95%CI [0.980, 0.997], p=0.000; Figures 5.4a-b). The line of equality represents perfect agreement between the measures (where x=y). Any data-points away from this line demonstrate a level of disagreement.

Figure 5.4a - Intra-rater Reliability using ultrasound for the measurement of VL muscle thickness

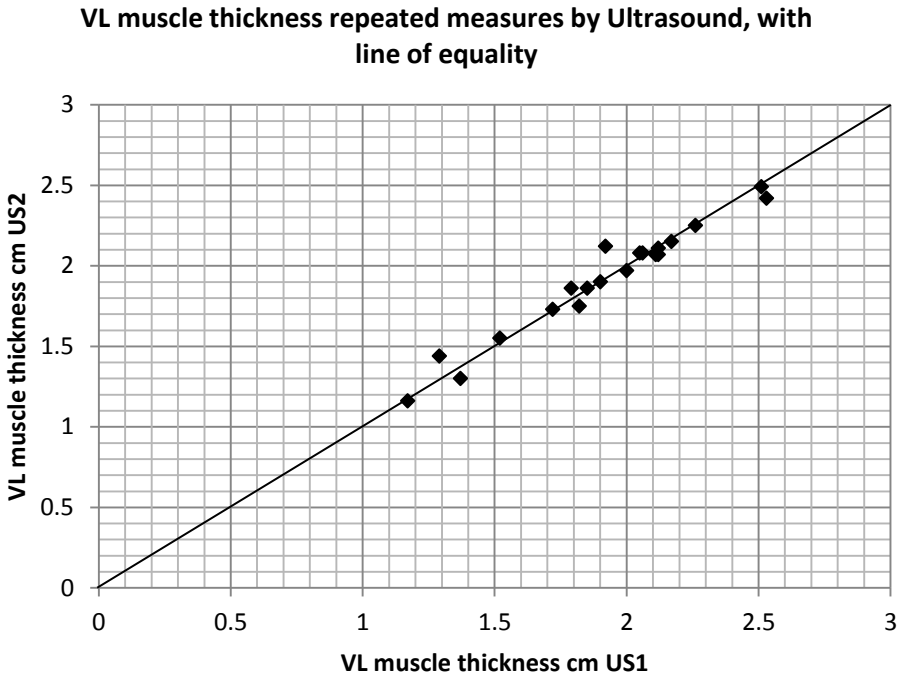


Figure 5.4b - Intra-rater Reliability using US for the measurement of fat thickness at the mid-VL point

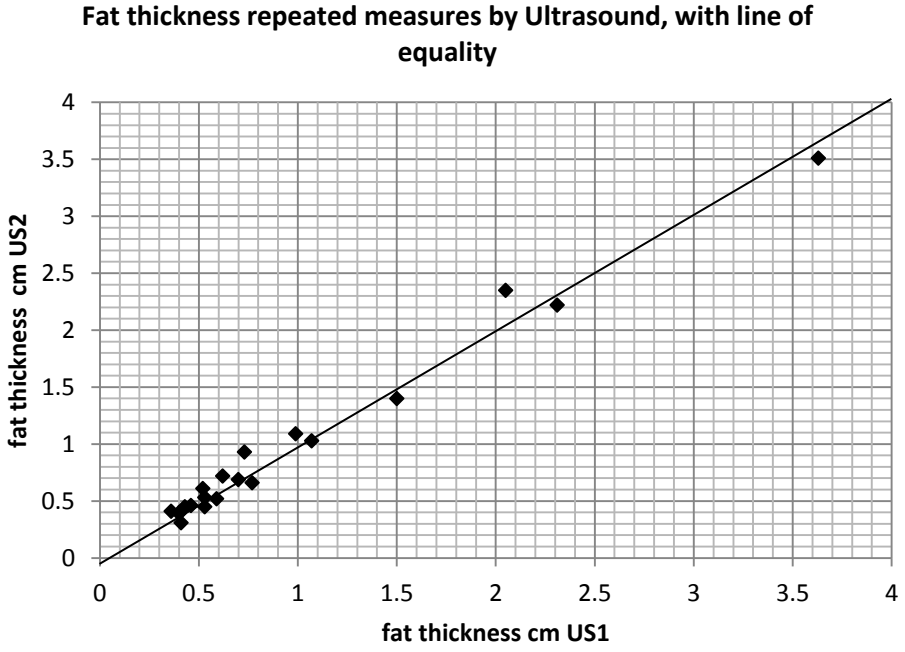


Table 5.3 summarizes the intra-rater reliability of Ultrasound measures of the vastus lateralis (VL) muscle thickness, and same site subcutaneous fat thickness.

Table 5.3 – Intra-rater reliability of ultrasound at mid-VL point (to two decimal places)

	N	US 1 (cm)	US 2 (cm)	ICC (95% CI)	Typical error (95% CI)	MDC (cm)
Mid-VL thickness (*cm*)	20	1.91 ± 0.37	1.92 ± 0.35	0.98 (0.95, 0.99)	0.05 (0.04, 0.07)	0.14
Total muscle thickness (*cm*)	10	1.83 ± 0.44	1.83 ± 0.42	0.97 (0.88, 0.99)	0.07 (0.05, 0.13)	0.19
Fat thickness (*cm*)	20	0.95 ± 0.83	0.96 ± 0.83	0.99 (0.98, 1.00)	0.08 (0.06, 0.11)	0.22

Presented as mean ± standard deviation; VL = vastus lateralis; US = ultrasound; ICC = intra-class correlation; MDC = minimal detectable change

5.3.3 Relationships between measures

Table 5.4 shows the relationships between the different measures of muscle and fat at the mid-VL site (VL ACSA, total muscle depth, VL-only depth, and fat depth).

Table 5.4 – Correlations between the different US-derived measures of muscle and fat and the mid-VL point

	Total muscle thickness	VL thickness	Fat thickness
VL ACSA	R=0.530 p =0.020 * n=19	R=0.582 p=0.009 ** n=19	R=0.305 p=0.204 n=19
Total muscle thickness		R=0.989 p=0.000 ** n=22	R=0.267 p=0.229 n=22
VL thickness			R=0.326 p=0.138 n=22

*Results presented as Pearson's r, significance, n; **significance is at the p<0.01 level (two-tailed), *significance is at the p<0.05 level (two-tailed); n = sample size used in analysis; ACSA = anatomical cross sectional area*

Table 5.5 describes the principal correlations between the measurements of muscle and fat using US and knee extension peak force (muscle strength). Relationships between body composition and strength measures showed good correlation between knee extension peak force (KE PF) and all muscle size measures using US.

Table 5.5 – Correlations between strength and US-derived measures of muscle and fat at the mid-VL point

	N	Mean ± SD	R
Knee extension peak force 45 (*Newtons*)	22	254.14 ± 108.00	KE PF45
ACSA (cm^2)	19	17.82 ± 2.82	0.61 (p=0.006**)
Total muscle thickness (*cm*)	22	3.58 ± 0.68	0.49 (p=0.022*)
VL thickness (*cm*)	22	1.93 ± 0.37	0.50 (p=0.018*)
Fat thickness (*cm*)	22	1.11 ± 0.99	0.23 (p=0.23)

Results presented as Pearson's r, significance

***significance is at the p<0.01 level (two-tailed), *significance is at the p<0.05 level (two-tailed); ACSA = anatomical cross sectional area; KEPF45 = knee extension peak force at 45 degrees*

The functional measure assessed (STS60) showed no significant correlations to any measure of muscle size or fat depth (p>0.1, n=20).

All muscle size measures showed significant relationships (p<0.05) to each other with very high correlations between the same measure, independent of method (MRI and US gave similar results; US or MRI ACSA r=0.96, p=0.000, n=19; VL thickness r=0.99, p=0.000, n=20). This suggests that either method could be used.

5.4 Discussion

5.4.1 Validity of US to MRI measures

The results of this study indicate that in comparison with MRI measurements, the use of 2-D B-mode ultrasonography (US) is a valid means of characterizing VL

muscle ACSA and thickness as well as subcutaneous fat at the same site in CKD5 patients receiving peritoneal dialysis therapy (Table 5.2).

The typical error in this study (Table 5.2) equates to 2.6% (VL ACSA), 1.8% (VL thickness) and 6.0% (fat thickness). This is in-line with previous US-MRI validation studies (in non-renal disease populations) that have used US to measure the quadriceps muscle (VL ACSA ICC 0.905, error 0.38cm^2, healthy participants, Ahtiainen et al 2010; VL ACSA ICC 0.999, healthy participants, Reeves et al 2004; 4.4% error against CT, coronary arterial disease patients, Thomaes et al 2012) and other sites (hip, ICC 0.81-0.89, healthy participants, Mendis et al 2010; lower trapezius, r=0.77, healthy/asymptomatic participants, O'Sullivan et al 2009).

US scans are able to clearly distinguish between muscle, fat, and connective tissue (Esformes et al 2002) and also allow accurate selection of measurement sites. This method can provide information on ACSA changes along the entire muscle length in response to training, disuse, and sarcopenia (Reeves et al 2004).

Given that clinical disturbances such as fluid accumulation and muscle wasting are very common in CKD, measures that can distinguish between tissues (unlike BMI, body mass, limb circumference) and accurately reflect excess body fat are very useful. The ability to quickly and accurately assess change in the CKD population may contribute to further explanations and associations with prognosis or mortality, such as ongoing research into the obesity paradox/reverse epidemiology (Morales & Praga 2012; discussed in Chapter 2, above).

5.4.2 Reliability and repeatability of US measures

In addition, the US measurements were found to be highly repeatable (Table 5.3) in this sample of patients.

Fluid status has been shown to affect reliability of body composition measurement techniques, but an earlier study in a very similar population (CKD patients also undergoing PD) has shown that multi-frequency (MF) BIA, DEXA, and skinfolds assessment all had much wider limits of agreement between methods (range 2.9±7.2% to 5.7±7.8%) (Konings et al 2003) than the repeated measures with US in this study.

Fat measurement error was greater and more variable (Table 5.3, repeatability, 10.0%) than VL muscle thickness using US (Table 5.3, VL depth 2.4%). The larger variation observed may in part be due to some compression of the subcutaneous fat beneath the probe during the procedure, but other studies have also found lower repeatability in measures of subcutaneous fat where participants were classed as overweight or obese (ICC 0.92, Bazzocchi et al 2011) as in this participant group (Table 5.1, BMI 27, range 20-39).

The reported ICC of repeated measures of VL muscle depth (0.98, Table 5.3) of the thigh is well within, and at the better end of the range of acceptable-to-excellent reliability seen in other studies of both healthy and unwell populations (ICC 0.72-0.99; Miyatani et al 2002; Matschke et al 2010b; Reeves et al 2004; Bemben 2002; Thoirs & English 2009; English et al 2012b). Previously, repeated measurement of ACSA have been reported with "good" reproducibility in young healthy subjects (ICC 0.87, rectus femoris, e Lima et al 2012); lower than the accuracy found in the direct depth measurement in this CKD5 patient study. The variation in error between VL muscle measures is small but notable; ACSA measurement error is marginally higher than measures of VL depth as there is more scope for the accumulated inflation of small errors during image collation.

The benefits of using US in cachectic patients to assess muscle quality and architecture have been previously alluded to (Matschke et al 2010b). Alongside the demonstrated validity and reliability of this method for CKD patients, US is clearly a

useful tool for comparative and interventional research studies, especially with the increased expediency of the US method and the reduction in participant burden (compared to other reference methods), the advantages are even more apparent.

5.4.3 Concurrent validity (relationship between measures of muscle size)

This study also investigated the relationship between the VL thickness and VL anatomical cross-sectional area (VL ACSA). Unsurprisingly, VL thickness, total muscle thickness, and VL ACSA are highly correlated with each other (Table 5.4, $p<0.05$), with VL thickness particularly well correlated to both total muscle and VL ACSA ($p<0.01$).

Using a thickness measure as an alternative to ACSA has been investigated in other studies and found to provide very similar degrees of correlation (and therefore information) with slightly better concordance in the lower extremities (upper thigh $r=0.922$-0.949, $p<0.001$, Ogawa et al 2012; mid-quadriceps, $r=0.91$, Abe et al 1997) compared to the arm muscles (mid-upper arm, $r=0.870$-0.915, $p<0.001$, Akagi et al 2008).

This highly significant correlation between these measures means a direct thickness measure might be able to provide acceptably similar information for monitoring and assessment purposes as the ACSA would. It is a more expedient process and measure in comparison to the more time-intensive image reconstruction and measurement of ACSA. By using one clear image at a single site, researchers and/or clinicians can minimize the risk of both measurement and processing errors.

5.4.4 Relationship between regional body composition and strength

The ability to measure regional body composition with greater accuracy and assess muscle size and structure by ultrasound (VL thickness, total muscle thickness, ACSA)

as a potential proxy for the measurement or assessment of strength (assessed here by knee extension peak force; KE PF) in CKD patients has not been extensively researched.

Knee extension requires significant quadriceps activity, especially at knee angles of 15-65° (where zero degrees is straight leg, or full knee extension), with the Vasti muscles being most predominantly used at angles less than 45° (Escamilla et al 1998). The KE PF45 assessed maximal strength at a 45° knee bend, and was significantly associated with each measure of the VL muscle size in this study (VL thickness $p<0.05$, total muscle thickness $p<0.05$, VL ACSA $p<0.01$, Table 5.5).

Associations between muscle size and maximal strength are well established, and often by adjusting results for an established measure of muscle size (e.g. muscle volume, anatomical and physiological cross sectional area; Bamman et al 2000) thereby assessing strength per unit of muscle, strength differences between population groups often disappear. Previous studies have assessed muscle size by way of volume, anatomical cross-sectional area (ACSA), physiological cross-sectional area (PCSA) and muscle layer thickness. In these, muscle ACSA has often demonstrated the most significant correlation to the strength measure used (tricep surae ACSA [r=0.733] and PCSA [r=0.715] were both better correlated/predictors of strength [maximal voluntary contraction] than volume [r=0.649], Bamman et al 2000), though authors of more recent publications have disagreed despite there being little difference in the results (muscle volume [r=0.760-0.926] better than ACSA [r=0.784-0.906] of elbow flexors, Akagi et al 2009; and the quadriceps [volume correlation 0.776, ACSA correlation 0.730], Blazevich et al 2009). In the present study, only the ACSA and thickness of the muscle of the quadriceps (at the mid-VL site) were examined and calculated to be correlated to maximal strength (knee extension peak force). In this study (Table 5.5), VL ACSA was shown to be most significantly correlated ($p<0.01$) closely followed by both the total muscle thickness and VL thickness ($p<0.05$). This suggests that the more extensive the information

available about the muscle size, the greater the correlation or predictive value potential.

5.5 Limitations

The greatest limitation of this study, apart from the small sample size, is the lack of information regarding the hydration status of the participants. With this additional information it may have been possible to account for some of the measurement error; oedema has been shown to fill the interstitial space between body tissues, rendering tissue boundaries less definite.

The decision to examine the mid vastus lateralis point allowed direct associations between muscle size and strength to be investigated. However, measuring the muscle and subcutaneous fat at only this site means the validity and reliability of US cannot necessarily be applied to all body-sites. In recent years, evidence has been accumulating on the negative effects of abdominal obesity and the relationship with the development of CKD (Cuppari 2013; Zoccali et al 2012) whether measured using gold standards tools (computed tomography in non-dialysed CKD; Kamimura et al 2013), or simpler methods such as waist circumference (CKD stages 1-4; Kramer et al. 2011) or waist-to-hip ratio (non-CKD at baseline; Elsayed et al 2008), and the long-term association with mortality (PD patients, Choi et al 2013).

Finally, the study only used one assessor when examining reliability and therefore the results are for intra-rater use alone. We do not know if another assessor (inter-rater) would show a similar level of accuracy in their measures. Generalization for use by a multitude of clinicians is not possible without further inter-rater reliability testing or training.

5.6 Conclusions

Valid assessment of regional body composition can be achieved via high-resolution ultrasound in CAPD CKD5 patients. In these patients there was high correlation between VL ACSA and VL muscle thickness in the axial plane, with all US measures highly repeatable and characterized by low measurement error.

VL thickness measured by US in the axial plane also has potential to be used as a marker of maximal strength (knee extension peak force at 45 degrees) and vice versa, though larger participant numbers are required to develop prediction equations or a reference sample for clinical use.

5.7 Implications for research

The validity and reliability of the US in repeated measures (in comparison to the gold standard MRI) could be applied to the general CKD population as the results are in line with previous studies in non-PD patients. However, the relationship between muscle size and strength may not be directly applied to other populations until a consensus has been agreed upon as to the differential wasting in the dialyzed population (greater differences between genders than between dialysis modality, van Biesen et al 2013).

CHAPTER 6 – Are whole and regional body composition indices, physical function, and uraemic symptoms related in non-dialysis dependent stage 3 CKD patients (NDD CKD3)?

6.1 Introduction

Observations from cross-sectional data (Table 4.4 and 4.6) have established that there is a deterioration in physical function and uraemic symptoms across the disease trajectory (from CKD3 to CKD5).

The clinical syndrome of uraemia is associated with fluid, metabolic abnormalities, electrolyte and hormonal imbalances which develop in parallel with deterioration of renal function, some of which start early in the disease trajectory (by CKD3) whereas others appear much later (reviewed by Fahal et al 2013). Using patient-reported uraemic symptom as a general guide to the progression of CKD, alongside the known increased frailty and dependence reported in the literature (Johansen et al 2013), it is likely that there would be a greater manifestation of symptom number, frequency, and intrusiveness into the life of a patient in the later stages of CKD than early to moderate stages. A study examining pre-dialysis CKD (stage 3b-4) patients observed the most commonly reported symptoms to be sleep disturbance, excessive tiredness and loss of muscle strength (Aulakh et al 2012), highlighting that muscle strength and exercise capacity are important contributors to the HRQoL and general well-being of patients with pre-dialysis CKD.

Other uraemic symptoms that appear early in the disease process include being easily fatigued, muscle stiffness, and spasms (Aulakh et al 2012). Fatigue, defined as the failure to sustain force of power output (Edwards et al 1981) is often reported by patients already on dialysis (Fahal et al 2013). However, people

with chronic kidney disease experience high levels of fatigue and are able to engage in fewer daily activities regardless of whether they are pre-dialysis (NDD) or are receiving either peritoneal or haemodialysis (Bonner et al 2010). A potential contributor to fatigue, more generalised wasting, and other common symptoms is the effect of loss of appetite in CKD. The loss of desire for food (defined as anorexia) is a commonplace symptom of uraemia in the CKD population, and typically develops when glomerular filtration rate (GFR) is 10-25% below normal and increases with the progression towards ESRD (Bergstrom et al 1999, Carrero et al 2009). This is possibly due to the retention of fluids and the reduced clearance rate (by the kidneys) of one or more appetite suppressants.

Health-related quality of life (HRQoL) is also distinctly reduced by end-stage renal disease (Amro et al 2014). Many studies have also suggested that HRQoL is already affected in "healthier" CKD patients, prior to the initiation of renal replacement therapy, implying that the initial decline originates at an earlier phase of the disease trajectory (comparing HRQoL using the Schedule for the Evaluation of Individual Quality of Life [SEIQOL] and LUSS; Pugh-Clarke et al 2006).

Protein energy wasting (PEW) is characterised by a decline in body protein mass and energy reserves and is an often underappreciated condition in early to moderate stages of CKD, despite it being a strong predictor of adverse outcomes (Kovesdy et al 2013). PEW is apparent in at least 20-25% of patients diagnosed with early to moderate CKD and increases as the disease progresses towards end-stage (dialysis-dependent) renal disease (Kovesdy et al 2013). The loss of body protein mass (and energy reserves) manifests as muscular atrophy, and generalised wasting, alongside fatigue, difficulty concentrating, and trouble sleeping (Novak et al 2008).

Although some previous studies have examined the body composition of patients earlier in the disease process (pre-dialysis) using gold standard techniques such as DEXA (Nielsen et al 1994) others have relied upon BIA (Avesani et al 2001, Bellizzi et al 2006, Carvalho et al 2012) but mainly using anthropometrics and skinfolds (Castaneda-Sceppa et al 2007, Carvalho et al 2012).

As previously mentioned (section 4.6) these tools are not able to distinguish between tissue (muscle and fat), and those that do (such as BIA) cannot comment on site-specific response to training, or other intervention, such as architectural adaptation (pennation angle, fibre length). Assessing muscle size and architecture in pre-dialysis patients using ultrasound is therefore important to establish the extent of wasting prior to the need for RRT.

6.1.1 Aims and Hypotheses

The previous study investigating validity and reliability of US (Chapter 5, above) clearly demonstrated that there are strong relationships between muscular isometric strength (measured by knee extensor peak force at 45 degrees) and US measures of the vastus lateralis (VL) muscle anatomical cross-sectional area (ACSA) and VL muscle depth in patients undergoing continuous ambulatory peritoneal dialysis (CKD5).

The aim of this study was to explore whether any relationships between body composition, physical function and uraemic symptom score were affected by the method of characterising body composition. It was hypothesized that strength and physical function would correlate positively with muscle size and architecture, and negatively with uraemic symptoms (LUSS).

6.2 Methods

6.2.1 Participants

All participants were recruited from a single hospital outpatient unit. These are the same cohort of CKD3 patients who volunteered for *Study 1* (Chapter 4, above).

All participants were informed of the protocol and procedures to be used and informed written consent was obtained from each, as approved by the appropriate local NHS Scientific Merit and Ethics Committee.

6.2.2 Assessments

Data collected previously included ultrasound (US) measures of the vastus lateralis (VL) muscle thickness (or depth) and muscle fibre pennation angle at the mid-VL point, total muscle thickness and fat thickness at the same site. Ultrasound images at the mid-VL site were taken in the sagittal plane (to observe muscle structure/architecture).

Anthropometric (mid-thigh and mid-arm circumference; section 3.3.1), strength (handgrip, knee extension peak force at 45 degrees, leg press peak force at 45 degrees; section 3.3.3), functional measures (sit-to-stand 5, sit-to-stand 60, North Staffordshire Walk test, physical activity recall; section 3.3.2), and health-related quality of life (Leicester Uraemic Symptom Score; section 3.3.4) were all collected as described previously (Chapter 3).

6.2.3 Statistics

Following normality checks (Shapiro-Wilks test) of the data distribution, standard statistical methods were used for the calculation of mean and standard deviations where appropriate.

Correlations between measures were calculated using Pearson's *r* in SPSS v21.0.

Significance (two-tailed) was set to be accepted at $p<0.05$.

6.3 Results

All data are presented as mean and standard deviation (*mean ± SD*), and to two decimal places (2dp), unless otherwise stated.

Participant demographics are shown in Table 6.1, and correlations in Tables 6.2-6.6.

6.3.1 Correlations (within assessment type)

6.3.1.1 Anthropometric measures (MTC, MAC)

There was a highly significant correlation between the two different anthropometric (MAC, MTC) measures (r=0.81, p=0.00, n=51).

6.3.1.2 Strength measures (KE PF 45, LP PF 45, handgrip)

Handgrip strength was highly correlated to peak isometric strength of the knee extensor muscles (KEPF45; r=0.79, p=0.00, n=39) and leg press peak force (LPPF45; r=0.68, p=0.00, n=47). Unsurprisingly, LPPF45 and KEPF45 were also significantly correlated (r=0.66, p=0.00, n=39).

6.3.1.3 Functional measures (STS5, STS60, NSRI walk test, PAR)

Sit-to-stand (functional) measures were significantly (negatively) correlated to each other, as would be expected (high STS60 and low STS5 is preferable; r= -0.72, p=0.00, n=48).

The walk test (NSRI) was also significantly correlated with both STS tests in CKD3. As with STS5, a low score (time in seconds) in the walk test is preferable, so the positive (highly significant) correlation between walk test and STS5 was expected (r=0.76, p=0.00, n=48), as was the negative (highly significant) correlation between STS60 and walk test (r= -0.65, p=0.00, n=46).

PAR was correlated to all other measures of strength ($r=0.32$-0.39, $p<0.05$, $n=39$-50) and function ($r=0.39$-0.41, $p<0.01$, $n=48$-50).

6.3.1.4 Health-related Quality of Life (Uraemic Symptoms)

Unsurprisingly, LUSS were highly correlated to each other; LUSS 2 (frequency) and LUSS 3 (intrusiveness) in particular (all correlates $r=0.57$-0.85, $p<0.01$, $n=51$).

6.3.2 Correlations between outcome measures

Correlations between outcome measures are shown in Tables 6.2, 6.4, and 6.5, with summary Tables (6.3 and 6.6)

Table 6.1 - Participant characteristics (CKD3: 30 ≤ GFR ≤ 59 mL/min)

		N	Mean ± SD *(1dp)*
Demographics	Age (*years*)	51	59.9 ± 13.9
	Height (*cm*)	51	165.2 ± 9.3
	Weight (*kg*)	51	77.3 ± 14.2
	BMI	51	28.1 ± 4.5
	Total body fat (*%*)	51	32.5 ± 9.0
Clinical measures	GFR (*mL/min*)	51	45.7 ± 7.0
	Hb (*g/dL*)	50	13.7 ± 1.8
	Albumin (*g/L*)	50	41.8 ± 3.0
	Serum Creatinine (*umol/L*)	50	162.1 ± 57.5
	CO_2 (*mmol/L*)	46	27.0 ± 3.3
	Urea (*mmol/L*)	49	15.1 ± 21.1
Ultrasound measures at mid-VL site	VL ACSA (cm^2)	42	17.5 ± 3.6
	VL depth (*cm*)	51	2.2 ± 0.4
	Total muscle depth (*cm*)	51	3.9 ± 0.7
	Fat depth (*cm*)	51	1.3 ± 1.0
	VL pennation angle (*degrees*)	43	16.1 ± 2.5
Anthropometry	Mid-arm circumference (*cm*)	51	33.8 ± 3.9
	Mid-thigh circumference (*cm*)	51	52.5 ± 5.9
Isometric muscle strength	Handgrip (*kg*)	50	27.4 ± 11.8
	KE PF 45 (*Newtons*)	39	303.7 ± 134.5
	Leg press peak force (*Newtons*)	47	267.1 ± 141.4
Physical Function and Activity	Sit-to-stand 5 (*secs*)	50	16.2 ± 10.9
	Sit-to-stand 60 (*count*)	48	21.9 ± 9.3
	NSRI walk test (*secs*)	48	102.1 ± 48.9
	Physical Activity Recall (*kcal/kg/day*)	51	35.4 ± 2.8
HR Quality of Life (Uraemic Symptoms)	LUSS 1 (*number*)	51	5.9 ± 2.4
	LUSS 2 (*frequency*)	51	14.5 ± 7.4
	LUSS 3 (*intrusiveness*)	51	8.5 ± 6.4

Table 6.2 – Relationship between US measures of subcutaneous fat, muscle size and architecture, with other routinely-used clinical outcome measures

	Anthropometry		Strength			Physical Function and Activity				HR Quality of life (uraemic symptoms)		
	MTC	MAC	KE PF 45	LP PF 45	Handgrip	STS5	STS60	NSRI walk	PAR	LUSS 1	LUSS 2	LUSS 3
VL ACSA	-0.20	-0.01	0.35 *	0.43 **	0.45 **	-0.03	-0.09	-0.23	0.09	- 0.04	- 0.06	0.06
(N)	(42)	(42)	(34)	(41)	(42)	(41)	(40)	(39)	(42)	(42)	(42)	(42)
Pennation angle	-0.36 *	-0.31 *	0.35 *	0.28	0.17	-0.33 *	0.45 **	-0.37 *	0.12	-0.42 **	- 0.46 **	- 0.51 **
(N)	(43)	(43)	(35)	(42)	(43)	(42)	(41)	(40)	(43)	(43)	(43)	(43)
VL depth	0.44 **	0.38 **	-0.12	0.30 *	0.08	-0.07	0.13 *	-0.07	0.18	- 0.03	- 0.07	0.08
(N)	(51)	(51)	(39)	(47)	(50)	(50)	(48)	(48)	(51)	(51)	(51)	(51)
Total muscle depth	0.50 **	0.53 **	0.13	0.30 *	0.31 *	-0.13	0.19 *	-0.20	0.25	0.06	- 0.01	0.06
(N)	(51)	(51)	(39)	(47)	(50)	(50)	(48)	(48)	(51)	(51)	(51)	(51)
Fat depth	0.67 **	0.41 **	-0.65 **	- 0.49 **	-0.67 **	-0.44 **	-0.42 **	0.35 *	-0.21	0.21	0.32 *	0.20
(N)	(51)	(51)	(39)	(47)	(50)	(50)	(48)	(48)	(51)	(51)	(51)	(51)

*Presented as Pearson's Correlation Coefficient (r) where * denotes significance at p<0.05, and ** at p<0.01, (N) is number of participants*

VL = vastus lateralis; ACSA = anatomical cross sectional area; MTC = mid-thigh circumference; MAC = mid-arm circumference; KEPF45/LPPF45 = knee extension/ leg press peak force at 45 degrees; STS5 = sit-to-stand 5; STS60 = sit-to-stand 60; NSRI walk = North Staffordshire Royal Infirmary walk test; PAR = physical activity recall; LUSS = Leicester Uraemic Symptom Score

Table 6.3 – Overview of significant correlations with US-derived measures of regional body composition at the mid-VL point

	VL ACSA *(cm^2)*	VL Pennation angle *(degrees)*	VL depth *(cm)*	Total muscle depth *(cm)*	Fat depth *(cm)*
Demographics	(-) Age * (-) Body fat % * (+) Height **	(-) BMI *	(-) Age ** (+) Weight ** (+) BMI **	(-) Age ** (+) Weight ** (+) Height ** (+) BMI **	(+) Body fat % ** (-) Height ** (+) BMI **
Anthropometry		(-) MTC * (-) MAC *	(+) MTC ** (+) MAC **	(+) MTC ** (+) MAC **	(+) MTC ** (+) MAC **
Clinical	(+) Hb **	(+) Hb *		(+) Hb * (+) serum Cr *	(-) Hb **
Isometric muscle strength	(+) Handgrip ** (+) KEPF45 * (+) LPPF45 **	(+) KEPF45 *	(+) LPPF45 *	(+) Handgrip ** (+) LPPF45 *	(-) Handgrip ** (-) KEPF45 ** (-) LPPF45 **
Physical Function and Activity		(-) STS5 * (+) STS60 ** (-) NSRI walk *	(+) STS60 *	(+) STS60 * (-) NSRI walk *	(+) STS5 ** (-) STS60 ** (+) NSRI walk *
HR Quality of Life (Uraemic Symptoms)		(-) LUSS 1 ** (-) LUSS 2 ** (-) LUSS 3 **			(+) LUSS 2 *

** significance at p<0.05, ** p<0.01, (+) positive correlation, (-) negative correlation; VL = vastus lateralis; ACSA = anatomical cross sectional area; MTC = mid-thigh circumference; MAC = mid-arm circumference; KEPF45/LPPF45 = knee extension/ leg press peak force at 45 degrees; STS5 = sit-to-stand 5; STS60 = sit-to-stand 60; NSRI walk = North Staffordshire Royal Infirmary walk test; PAR = physical activity recall; LUSS = Leicester Uraemic Symptom Score; Hb = haemoglobin; BMI = body mass index*

Table 6.4 – Relationship of HR QoL (uraemic symptoms; LUSS) with patient demographics and selected clinical variables

	Basic demographics					Clinical measures				
	Age	Weight	Height	BMI	Body fat %	Hb	Albumin	Serum Cr	CO_2	Urea
LUSS 1 (number)	- 0.33 *	0.18	- 0.10	0.24	0.11	- 0.09	- 0.10	- 0.23	- 0.03	0.03
(N)	(51)	(51)	(51)	(51)	(51)	(50)	(50)	(50)	(46)	(49)
LUSS 2 (frequency)	- 0.17	0.25	- 0.17	0.41 **	0.28 *	- 0.17	- 0.10	- 0.16	- 0.01	- 0.05
(N)	(51)	(51)	(51)	(51)	(51)	(50)	(50)	(50)	(46)	(49)
LUSS 3 (intrusiveness)	- 0.11	0.30 *	- 0.10	0.42 **	0.20	- 0.16	- 0.07	-0.08	- 0.07	- 0.00
(N)	(51)	(51)	(51)	(51)	(51)	(50)	(50)	(50)	(46)	(49)

*Presented as Pearson's Correlation Coefficient (r) where * denotes significance at p<0.05, and ** at p<0.01, (N) is number of participants; LUSS = Leicester Uraemic Symptom Score; Hb = haemoglobin; BMI = body mass index; CO_2 = carbon dioxide in blood serum*

Table 6.5 – Relationship of patient-reported uraemic symptoms (LUSS) with other routinely-used clinical outcome measures

	Anthropometry		Strength measures			Functional measures			
	MTC	MAC	KE PF 45	LP PF 45	Handgrip	STS5	STS60	NSRI walk	PAR
LUSS 1 (number)	0.27	0.31 *	- 0.19	-0.08	-0.04	0.21	-0.26	0.13	0.01
(N)	(51)	(51)	(39)	(47)	(50)	(50)	(48)	(48)	(51)
LUSS 2 (frequency)	0.39 **	0.40 **	-0.33 *	-0.23	-0.15	0.46 **	-0.52 **	0.40 **	-0.14
(N)	(51)	(51)	(39)	(47)	(50)	(50)	(48)	(48)	(51)
LUSS 3 (intrusiveness)	0.40 **	0.35 *	-0.27	-0.16	-0.10	0.39 **	-0.49 **	0.35 *	-0.12
(N)	(51)	(51)	(39)	(47)	(50)	(50)	(48)	(48)	(51)

*Presented as Pearson's Correlation Coefficient (r) where * denotes significance at p<0.05, and ** at p<0.01, (N) is number of participants*

LUSS = Leicester Uraemic Symptom Score; MTC = mid-thigh circumference; MAC = mid-arm circumference; KEPF45/LPPF45 = knee extension/ leg press peak force at 45 degrees; STS5 = sit-to-stand 5; STS60 = sit-to-stand 60; NSRI walk = North Staffordshire Royal Infirmary walk test; PAR = physical activity recall

Table 6.6 – Overview of factors significantly associated with patient-reported uraemic symptoms

	LUSS 1 (*number*)	LUSS 2 (*frequency*)	LUSS 3 (*intrusiveness*)
Basic	(-) age *	(+) BMI ** (+) body fat % *	(+) weight * (+) BMI **
Clinical			
US measures at mid-VL point	(-) pennation angle **	(+) fat depth * (-) pennation angle **	(-) pennation angle **
Anthropometry	(+) MAC *	(+) MTC ** (+) MAC **	(+) MTC ** (+) MAC *
Strength		(-) KEPF45 *	
Function		(+) STS5 ** (-) STS60 ** (+) NSRI walk **	(+) STS5 ** (-) STS60 ** (+) NSRI walk *

** significance at p<0.05, ** p<0.01, (+) positive correlation, (-) negative correlation*

VL = vastus lateralis; MTC = mid-thigh circumference; MAC = mid-arm circumference; KEPF45/LPPF45 = knee extension/ leg press peak force at 45 degrees; STS5 = sit-to-stand 5; STS60 = sit-to-stand 60; NSRI walk = North Staffordshire Royal Infirmary walk test; PAR = physical activity recall; LUSS = Leicester Uraemic Symptom Score; Hb = haemoglobin; BMI = body mass index

6.4 Discussion

It was hypothesized that strength and function would be positively correlated with muscle size and architecture, and negatively with uraemic symptoms. Uraemic symptoms were indeed negatively correlated with both strength and function (the greater the reported frequency and intrusiveness of the symptoms, the weaker and less functional the participants were). However, the relationships between US-derived measures of muscle size and architecture, with objectively measured strength and function were more complex (Table 6.3).

Patient-reported uraemic symptoms assessed using the Leicester Uraemic Symptom Score (LUSS) were significantly correlated to pennation angle of the VL muscle at the mid-VL point (LUSS1 p=0.005, LUSS2 p=0.002, LUSS3 p=0.000) in CKD stage 3 patients. The negative relationships (Table 6.2) indicate that improved muscle architecture (larger pennation angle) is correlated with lower LUSS scores (fewer and less frequent or intrusive symptoms) and thus assumed better quality of life.

There were no significant correlations in this population between patient-reported uraemic symptoms and clinical measures (Table 6.6). This suggests that patient perception of muscular weakness, fatigue, and other uraemic symptoms in CKD are largely unrelated to clinical measures of renal function; this has also been observed in other samples (CKD stage 3b-4; Aulakh et al 2012). Despite the association of haemoglobin (Hb) with muscle size and architecture (Table 6.3) and with physical performance measures (Aulakh et al 2012), the lack of association between uraemic symptoms and clincical measures is interesting, and may warrant further investigation considering psychological and lifestyle factors as well as individual and group co-morbidities.

6.4.1 Ultrasound-derived measures of body composition

This is the first study to explore the relationship between patient-reported uraemic symptoms (as an indication of HRQoL) and muscle size and architecture using ultrasound in CKD patients, especially outside of the renal replacement (dialysis) therapy population.

6.4.1.1 Muscle size (VLACSA, VL depth, total muscle depth) and architecture (pennation angle)

Muscle size was significantly correlated to age, demonstrating that an older individual has reduced muscle mass, as would be expected based on recent data in healthy populations (quadriceps thickness, Strasser et al 2013). It was also observed in the same research study (Strasser et al 2013) that in younger populations, quadriceps muscle thickness is significantly correlated with BMI (as observed here, Table 6.3).

Pennation angle is important in CKD as it represents the health or quality of the muscle, and potential force production. This is reflected in the results that pennation angle is well correlated to measures of function (STS5, STS60, and NSRI walk; Table 6.3) and strength (KEPF45, Table 6.3); however, the non-significant correlations with LPPF45 (r=0.28, p=0.07, n=42) and handgrip strength (r=0.17, p=0.26, n=43) were surprising.

Based on the correlations presented in Table 6.3, it appears that muscle architecture (pennation angle) is more related to functional performance (r=0.33-0.45) whereas muscle size (VL ACSA) is a stronger predictor of maximal strength (r=0.35-0.45). John et al (2013) reported poor correlation between change in muscle size (cross-sectional area) and change in functional ability too. This may

suggest that even with reduced muscle size, functional performance could be maintained so long as quality of the muscle is maintained (muscle pennation angle remains wide). Other research in dialysis patients has documented reduced muscle force, selective structural changes and significant muscle wasting in the presence of normal skeletal muscle physiology (Fahal et al 1997), once again indicating that loss of muscle mass is linked more to loss of strength than change in architecture, and that detrimental changes in muscle architecture may occur later in the disease process, alongside the reduction in functional ability.

6.4.1.2 Fat depth

Fat depth has most correlations when examining all outcome measures, but may be due to the fact that most of the composition assessments can be driven by fat more than muscle (BMI, % body fat, MTC, MAC). However, fat also has the most significant correlations with strength and function. It has been suggested previously that retaining greater adiposity is advantageous in the CKD population, which may be due to the theory that fat is muscle-saving (Ikizler 2008). However, the relative influence of fat mass or muscle mass on the obesity paradox (where greater BMI in dialysis patients appears to confer lower hazard ratio for mortality) is difficult to evaluate because of limited epidemiologic evidence, unclear mechanistic processes to explain the obesity paradox, and the lack of definitive evidence from intervention studies (Park et al 2014).

Fat depth and KEPF45 are negatively (and highly significantly) correlated in this sample of CKD3 patients ($r=-0.63$, $p=0.00$, $n=39$). However, this is in contrast with the previous study where $r=0.23$, $p=0.23$, $n=22$ (Chapter 5). Admittedly, the previous study used significantly sicker patients (CKD5, already undergoing peritoneal dialysis for an average of 30-months; Table 5.1) than in this study;

though other than the disease stage, other demographics were markedly similar (age, weight, BMI; Table 5.1).

6.4.2 Health-related Quality of life (uraemic symptoms)

The number of patient-reported uraemic symptoms (LUSS 1) is (significantly) negatively correlated with age, indicating that the older the individual, the fewer uraemic symptoms they seem to report. This may be as many of the symptoms listed are often associated with the general ageing process (e.g. pain in joints/bones, loss of muscle strength/power, poor concentration/mental alertness) and so may not have appeared noticeably worse to the patients. This has been observed in a both the healthy and ill populations, and the literature describes an expected annual loss in strength (maximal voluntary contraction) of approximately 1.5% per year after the age of fifty (Strasser, 2013; Doherty 2003; Ivey et al 2000; Lauretani et al 2003). Additionally, it has been observed in the wider community that older individuals tend to complain (report pain, weakness, and fatigue) less than younger individuals as they believe it to be an expected result of ageing (Avlund et al 2007; Rush et al 2013).

Correlations show higher reported frequency (LUSS 2) and intrusiveness (LUSS 3) of uraemic symptoms linked with reduced strength and function (Table 6.5), increased fat percentage, BMI (Table 6.4), and lower muscle quality (pennation angle, Table 6.2). These are also observably common results of the ageing process (Scott et al 2011). Data regarding which of the listed uraemic symptoms were most commonly reported in this sample of early stage CKD patients was not analysed, limiting the ability to discuss the nature of the correlations more directly. If it is assumed that the most prevalent reported were in line with previous reports - (1) sleep disturbance; (2) excessive tiredness; (3) loss of strength; (4) itching; (5) muscle stiffness and (6) restless legs (Aulakh et al 2012) - then the correlation with muscle

size and structure, and the previously established relationship with strength and function, becomes clearer.

6.5 Study Limitations

The two main limitations of this study are (1) the relatively small sample size, and (2) it was not possible for all outcome measures to be obtained across the entire sample. For a study of correlations between measures, a larger sample would be preferable to allow correction for factors such as age, BMI, or even strength or functional results. However, the fifty-one participants were closely mixed by gender (28M:23F) and were representative of the average CKD3 population (borderline between CKD stages 3a and 3b).

6.6 Implications for research

Examining correlations between outcome measures allows the research community to potentially use one measure as a proxy (in repeated measure) for another in the event that certain data is not collected (eg. BMI for body fat percentage, education level for cognitive ability), this is routinely done by clinicians and researchers alike (Clinton 2004). In this exploratory correlational study, sit-to-stand-60 was well (negatively) correlated to patient-reported uraemic symptoms (LUSS2, frequency, r=0.52; LUSS3, intrusiveness, r=0.49) as was pennation angle of the VL muscle (STS60, r=0.45, LUSS1, number, r=0.42, LUSS2, frequency, r=0.46, LUSS3, intrusiveness, r=0.51). To determine whether these could be used as proxy measures would require further testing in a larger sample.

6.7 Conclusions

There are significant and relatively strong correlations between patient-reported (perceived) uraemic symptoms and objectively measured strength, function and regional body composition (site-specific muscle size and quality) in pre-dialysis CKD (stage 3) patients. Recently a two year follow-up study observed greater muscle mass loss in pre-dialysis patients than those already undergoing dialysis at study initiation (John et al 2013). Therefore, intervening early (pre-dialysis) to hinder this accelerated loss of muscle - and consequent loss of strength and/or function on the road to frailty - is vital in this population.

Having established the relationships between the manifestations of chronic kidney disease symptoms, such as muscle wasting, loss of strength, and other such uraemic symptoms assessed by the quality of life measure (LUSS) in this study, it is necessary to test whether an anabolic intervention (such as resistance training) can affect these symptoms, and whether the response will be quantifiably the same across the complete array of uraemic symptoms (i.e. will a ten percent increase in strength equate to a ten percent improvement in uraemic symptoms score).

CHAPTER 7 – Does frequency of (resistance) exercise training influence outcome over a 12-week period in people with stage 3 Chronic Kidney Disease (CKD3)?

7.1 Introduction

Frailty is observably more common in individuals with CKD than those without (Johansen et al 2013). Additionally, frailty in moderate to severe CKD is more common than in other chronic illnesses such as vascular disease, cancer, and other degenerative diseases of ageing (Wilhelm-Leen et al 2009). Risk of frailty is increased by approximately 2-times in mild CKD (stages 1-3a) and 6-times in moderate to severe (stages 3b-5) CKD (Wilhelm-Leen et al 2009) and is associated with increased incidence of adverse outcome in dialysis patients (increased hospitalisation, increased death rate; Johansen et al 2013; Kosmadakis et al 2010).

CKD patients that have been defined as frail are started on dialysis on average much earlier (i.e. at a higher estimated glomerular filtration rate, eGFR) than those deemed non-frail (Johansen et al 2013) and sadly the deterioration trajectory is increased from dialysis initiation, as higher levels of dependence in performing activities of daily living (ADLs) are recorded in these patients (Kurella-Tamura et al 2010). This demonstrates the need to intervene early to slow the decline into "frailty", and therefore delay these patients being transferred onto maintenance dialysis, and protect their independence for longer.

The need for additional protein to overcome the negative balance and malnutrition cannot be solved by simply increasing protein intake in food, as this in turn can aggravate uraemia (Workeneh & Mitch 2010). Therefore anabolic interventions to increase protein production and reduce loss are vital.

In healthy individuals, resistance training is a proven anabolic intervention with long-term benefits (Ikizler 2011). Using resistance training to maintain function has been recommended for frail elderly populations whose strength levels may become a greater limiting factor for their activities of daily living than their cardiac function (Pendergast et al 1993; Hurley et al 2011). Additionally, maintaining optimal muscle mass and function with ageing plays an important role in preventing or delaying the onset of chronic diseases and critical illness (Wolfe 2006; Hurley et al 2011), often highlighted through a reduced need for medical intervention (Cawthon et al 2009; Suetta et al 2007).

Resistance training (RT) has also been reported to reduce muscle catabolism and counteract weight loss and malnutrition (assessed by total body potassium and leucine oxidation) in pre-dialysis CKD4 patients (Castaneda et al 2001, 2004), and corrected protein synthesis, reduced muscle proteolysis (breakdown), and increased muscle progenitor cell number and activity (compared to treadmill running which only corrected/reduced muscle proteolysis) in CKD mice (Wang et al 2009). Despite it being recommended that RT be initiated early in the pre-dialysis stage (Kouidi 2002; Clyne 2004) there are very few published reports of RT in pre/non-dialysis dependent (NDD) patients.

Resistance training has been introduced in mixed/combination and strength-specific interventions in end-stage renal disease (CKD5) patients undergoing dialysis (Chapter 2, Table 2.6.) where strength, function, and muscle mass is already massively reduced in comparison to earlier in the disease process (pre-dialysis). The results of these later studies have demonstrated beneficial and statistically significant changes in muscle size, strength and function to the participants (Dong et al 2011; Chen et al 2010; Cheema et al 2006, 2007).

A systematic review of exercise interventions in CKD highlighted the lack of RCTs investigating resistance training, as most research to date has focused on cardiovascular programmes (Heiwe & Jacobson 2011). The authors commented that resistance training had a significant beneficial effect on muscular strength but there were too few included studies (in the meta-analysis) using cardiovascular exercise or mixed cardiovascular and resistance training, to be able to draw conclusions concerning the type of exercise required for optimal enhancement of muscular strength. There is also great variability in the results of these studies as they implemented different programmes (varying session duration, exercise intensity, intervention length, and exercise modality) and assessed and reported results using a variety of measures for similar outcomes (Heiwe & Jacobson 2011).

In order to develop and prescribe the most effective exercise intervention programme for CKD patients, further research needs to be undertaken into exercise mode, frequency, and intensity (Smart et al 2013), to elucidate the greatest or most efficient dose-response relevant to the CKD population.

There appears to be little information in the published literature regarding the associations between muscle size (thickness, cross-sectional area), architecture (pennation angle), function (force, sit-to-stand, walk tests), and the self-reported score of uraemic symptoms by the patient, or the possibility for improvements/change through an intervention programme, whether exercise, nutritional, or pharmacologically based. Indeed, a literature search revealed few studies examining changes in the reporting of number, frequency, or intrusiveness of uraemic symptoms from an intervention, apart from at the initiation of dialysis as part of the usual care-process (improved symptom scores using the Pittsburgh Symptom Score Index over the 12-months following initiation of peritoneal dialysis; Novak et al 2008) and a prospective comparative study in which CKD4 and CKD5

pre-dialysis patients who undertook an exercise programme also recorded a significant reduction in uraemic symptoms using the Leicester Uraemic Symptom Score after one-month of activity, maintained to six-months (Kosmadakis et al 2012).

7.1.1 Summary

The loss of muscle mass and strength are important determinants of survival in CKD (Bonanni et al 2011) and a variety of other chronic illnesses (cardiac failure, Anker et al 2004; cancer, Kadar et al 2000; sarcopenia, Metter et al 2004; Morley et al 2009), and an anabolic intervention (resistance training) may have an effect on the progression of CKD-related protein-energy wasting through the modification of risk factors such as malnutrition (negative protein balance), inflammation, and physical inactivity.

The response to an exercise intervention with pre-dialysis CKD patients has been shown to be equal to the response in non-CKD (healthy) age-matched controls, unlike patients later in the disease-process who may be limited in their improvement in strength and function (Heiwe et al 2001). Therefore intervening in pre-dialysis stages has the greatest potential for large improvements that would be beneficial to the patient; to potentially hinder the progression of protein-energy wasting (rat studies, Heifets et al 1987; Osato et al 1990), and related functional decline.

7.1.2 Study aims and hypotheses

The aim of this study was to investigate the effectiveness of resistance training as a countermeasure to the established muscle wasting associated with chronic kidney disease (Hurley et al 2011). The secondary aim was to explore the effects of

training frequency upon the individual's body composition, regional muscle size and architecture, and associated strength and functional capacity, as well as any changes and associations between these measures and the self-reported uraemic symptoms in these pre-dialysis CKD3 patients.

It was hypothesized that the effects of exposure to the intervention (resistance training programme) once per week (RT1) would be significantly different from those patients exposed three times per week (RT3), due to an established dose-response relationship (RT3>RT1).

7.2 Methods

7.2.1 Participants

Forty-five consecutively presenting CKD3 patients were approached at a routine outpatient clinic. Twenty-eight patients initially showed interest in participating and received information packs including participant information sheet, informed consent form and investigator contact details. Twenty-two returned the informed consent and agreed to attend for pre-randomisation assessments. Twenty patients took part in the baseline assessments (Figure 7.1, participant flow).

Pre-randomisation (baseline) assessments took place at the Renal Rehabilitation gymnasium at a UK National Health Service University Hospital. All assessments were made by a single investigator and included measurement of (1) whole body composition; (2) regional body composition; (3) muscle architecture; (4) neuromuscular performance, including peak isometric strength; (5) physical function; and (6) uraemic symptoms.

Following these assessments, participants were randomly assigned using a computerised block randomisation programme to either a low frequency (one session per week, RT1) or higher frequency (three sessions per week, RT3)

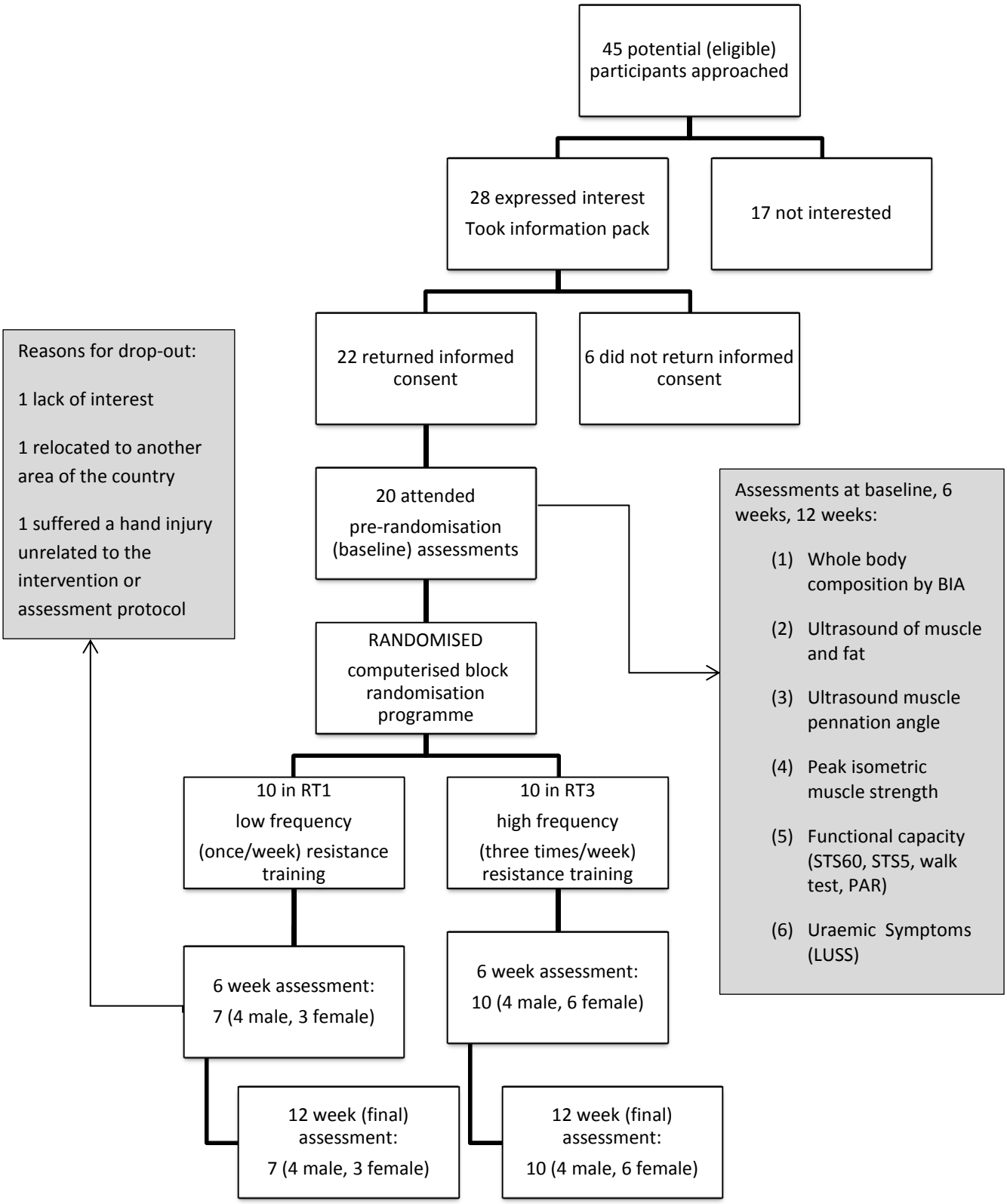
resistance training group. Participants in both groups completed a 12-week programme of lower extremity strengthening exercises.

7.2.2 Intervention

Each supervised training session consisted of a short (five minute) aerobic warm-up on a mechanically braked cycle ergometer (Monark, Sweden) followed by a series of lower extremity exercises using fixed weight machines (knee extension, leg press, calf raise, hamstring curl) and bodyweight-resisted exercises (lunges, squats). In each session participants completed 3 sets of 8 repetitions at 80% of the individual's one rep max (80% 1RM).

Progression/adaptation: 1-RM was amended as required (when an individual could surpass the prescribed dose of 3 sets of 8 repetitions). The results of the fortnightly measure of leg press and knee extension peak force were used as a guide for advancement and progression.

Figure 7.1 - Participant flow through and assessment phasing in the intervention study



7.2.3 Assessments

All participants returned to the Renal Rehabilitation gym after 6 and 12 weeks for follow-up assessments. Additionally, all participants had their regional body composition and neuromuscular function (strength) assessed every two weeks. These additional assessments always preceded their participation in the first exercise session of the week (RT3 group), or their only session of the week (RT1 group).

All outcome measures were taken by a single assessor (blinded to group allocation) highly experienced in ultrasonography, anthropometry, and measures of physical strength and function, in both a clinical and laboratory setting.

7.2.3.1 Body composition

Body mass index (BMI) was calculated using [weight (kg)/height (metres)^2]. Measurements of regional body composition were taken with participants lying in a supine position for a minimum of 20 minutes to allow for any fluid shifts prior to assessment. Whole body multi-segmental bioelectrical impedance spectroscopy/analysis was used to measure total body water, fat and fat free mass according to the procedures described in the General Methods (Chapter 3).

7.2.3.1.1 Regional body composition and muscle architecture (fortnightly)

Remaining in a supine position throughout, participants were instructed to relax the muscle being assessed. Knee extension angle was kept at zero degrees of flexion (straight leg).

Ultrasound measurements of the vastus lateralis (VL) muscle thickness/depth, VL subcutaneous fat thickness/depth, VL anatomical cross-sectional area (VL ACSA), VL pennation angle, triceps brachii muscle thickness/depth, tricep brachii

subcutaneous fat thickness/depth were obtained using a 50mm, 7.7MHz linear array probe (Sonosite® 180 plus, Sonosite Inc., USA).

VL muscle and subcutaneous fat thickness/depth and pennation angle measures were taken at 50% femur length and mid-VL width. Images were taken with the probe perpendicular to the dermal surface of VL along the mid-sagittal line of the VL. Fascicle length was calculated using the equation

$$Fascicle\ length\ =\ [\ VL\ Mth/\sin\Theta\ ]$$

VL ACSA images were taken in the axial plane and were recorded onto SVHS videotape and acquired via individual frame capture software (Adobe Premier v5.1, Adobe Systems). Using lines cast by external markers, scans were fitted to form a reconstructed full image using a contour matching programme (ImageJ). VL ACSA was then measured via an image analysis programme (NIH Image v1.6, NIH, MD, USA).

7.2.3.2 Neuromuscular performance - Strength (fortnightly)

Muscle strength was assessed using a handgrip dynamometer (Lafayette Instrument, Lafayette, IN), Knee Extension peak isometric force and Leg Press peak isometric force, assessed at 45° (Gleeson et al 2002; Chapter 3, above). Results for each measure were based on the best of three attempts on the dominant side.

7.2.3.3 Functional capacity (six-weekly)

Sit-to-stand 60 (STS60, number of complete sit-to-stand movements within 60 seconds) and sit-to-stand 5 (STS5, time taken to complete five sit-to-stand movements) were performed from a standard chair height of 0.42 metres.

The NSRI walk test (North Staffordshire Royal Infirmary walk test, Mercer et al 1998) involved a walk of 50-metres, a stair climb of 22 steps (3.3-metre elevation, individual step height 15cm), the same stair descent, and 50-metre walk back to the start. Time was recorded in seconds.

Participants were also asked to recall their physical activity over the last week (Physical Activity Recall; Blair et al 1985).

7.2.3.4 Uraemic Symptoms (six-weekly)

Uraemic symptoms affecting health-related quality of life were measured using the Leicester Uraemic Symptom Score (LUSS; Wright & Stein 1993). LUSS is a five-point Likert scale that evaluates symptom number (LUSS 1), frequency (LUSS 2) and intrusiveness (LUSS 3) of a selection of eleven symptoms commonly associated with kidney problems (sleep disturbance, muscle spasm/stiffness, excessive tiredness, pain in joints/bones, loss of muscle strength/power, poor concentration/mental alertness, restless legs, impotence/lack of sex drive, shortness of breath, itching, and loss of appetite).

7.2.4 Statistics

Following screening of data for normality, standard statistical methods were used for the calculation of mean and standard deviations. Group comparison (RT1 vs RT3) at baseline was assessed by Student's unpaired t-test for all measures.

Mixed model repeated measures ANOVA (3x2) was employed (SPSS v21.0) to assess time and group effect and interactions.

Data are reported as mean ± standard deviation unless otherwise stated.

Statistical significance was accepted at $p<0.05$.

7.3 Results

There were no significant baseline differences ($p>0.05$) in the demographic and physical characteristics of the groups completing the study (Table 7.1).

Table 7.1 – Participant characteristics at baseline (t_0)

	RT1	RT3
Sample size *n* (M:F)	7 (4:3)	10 (4:6)
Age (*yrs)*	52.9 ± 16.5	59.7 ± 9.9
(*range*)	*(34 – 76)*	*(44 – 73)*
Weight (*kg)*	79.4 ± 9.1	75.8 ± 16.7
BMI *(kg/m^2)*	29.7 ± 4.7	27.3 ± 4.1
% fat	35.4 ± 11.7	33.25 ± 9.0
Fat mass (*kg)*	28.3 ± 10.4	25.0 ± 8.5
FFM (*kg)*	51.1 ± 9.3	50.8 ± 14.1
TBW (*litres)*	37.4 ± 6.8	37.2 ± 10.3
CCr (*mL/min)*	49.1 ± 9.6	47.1 ± 6.5
SerumCr (*umol/L)*	135 ± 87	176 ± 45.5
Urea (*mmol/L)*	11.2 ± 6.3	15.0 ± 4.6
Albumin (*g/L)*	42.7 ± 2.2	40.5 ± 2.7
Hb (*g/dL)*	13.7 ± 1.4	13.0 ± 2.0
CO_2 (*mmol/L)*	28 ± 2.3	26.4 ± 2.6
GFR (*mL/min)*	36.1 ± 12.9	36.6 ± 15.8

Presented as mean ± standard deviation; BMI = body mass index; FFM = fat free mass; TBW = total body water; CCr = creatinine clearance; Hb = haemoglobin; CO_2 = carbon dioxide in blood serum; GFR = glomerular filtration rate

7.3.1 Upper body "control data" to assess potential systemic effects related to any dietary change

Measurements of upper arm muscle thickness, subcutaneous fat, and handgrip strength were made immediately prior to and following the 12-week intervention period. This data was collected as a form of "verification control" check to ensure that any adaptation due to change in nutritional status or pathophysiology was reflected at a body-site not involved in the lower body resistance training intervention.

No significant differences were observed between RT1 and RT3 groups (Table 7.2). Measures of upper body strength (handgrip dynamometry) and upper arm muscle thickness (bicep brachii and tricep brachii muscle depth) showed no significant change over the 12-week period (tendency for triceps muscle to reduce in size). There was however a significant decrease in subcutaneous tricep fat depth ($p=0.02$, t_0: 2.17 ± 0.99 cm, t_6: 2.05 ± 0.98 cm, t_{12}: 2.04 ± 0.97cm) with a similar trend evident in subcutaneous bicep fat depth (trend, $p=0.09$, t_0: 1.80 ± 0.78 cm, t_{12}: 1.50 ± 0.69 cm).

Table 7.2 - Changes in upper arm muscle thickness/depth, upper arm subcutaneous fat thickness/depth, and handgrip strength across the 12-week intervention period

	RT1 t_0	RT1 t_{12}	RT3 t_0	RT3 t_{12}	Time effect (*p*-value)
Handgrip (*kg*)	25.9 ± 11.3	26.1 ± 10.7	28.5 ± 12.2	29.1 ± 13.5	Ns
Tricep brachii depth (*cm*)	4.3 ± 0.8	4.1 ± 0.8	3.9 ± 0.8	3.6 ± 0.9	Ns
Tricep fat depth (*cm*)	2.2 ± 1.2	2.2 ± 1.2	2.1 ± 0.8	1.9 ± 0.8	0.02
Bicep brachii depth (*cm*)	2.8 ± 0.8	2.8 ± 0.8	2.9 ± 0.6	2.9 ± 0.7	Ns
Bicep fat depth (*cm*)	1.9 ± 0.8	1.7 ± 0.8	1.7 ± 0.8	1.3 ± 0.6	Ns

Presented as mean ± standard deviation; Ns = non-significant result

Measures of upper body strength, fat, and muscle showed no beneficial change in muscle size or strength over the 12-week intervention, providing some reassurance that changes detected in the primary outcome measures might reasonably be attributed to the intervention, not other systemic effect mediated changes.

7.3.2 Body composition

There was no statistically significant interaction for measures of whole body composition assessed by Bioelectrical Impedance Analysis (Table 7.3, $p>0.05$). There was also no significant group effect.

Weight increased steadily over the 12-weeks in both groups, but did not quite reach statistical significance ($p=0.051$, t_0: 77.29 ± 13.84 kg, t_{12}: 78.49 ± 13.42 kg, Table 7.3). This was probably driven by the (statistically non-significant, $p>0.05$) increase in FFM of RT3 (2.1kg); three times that of RT1 (0.7kg).

Table 7.3 - Total body composition measurements (by Bioelectrical Impedance) throughout the 12-week study period

	RT1 t_0	RT1 t_{12}	RT3 t_0	RT3 t_{12}
Weight (*kg*)	79.4 ± 9.1	81.1 ± 9.9	75.8 ± 16.7	78.1 ± 15.9
BMI (kg/m^2)	29.7 ± 4.7	30.3 ± 4.6	27.2 ± 4.1	28.1 ± 3.6
Fat (*%*)	35.4 ± 11.7	36.0 ± 10.9	33.3 ± 9.0	32.6 ± 10.6
Fat mass (*kg*)	28.3 ± 10.4	29.5 ± 9.6	25.0 ± 8.5	25.3 ± 9.4
FFM (*kg*)	51.1 ± 9.3	51.8 ± 9.0	50.8 ± 14.1	52.9 ± 14.5
FFM (*ratio*) *Truncal/ appendicular*	1.20 *27.9 / 23.2*	1.18 *28.0 / 23.7*	1.25 *28.2 / 22.6*	1.24 *29.3 / 23.6*
TBW (litres)	37.4 ± 6.8	37.8 ± 6.7	37.2 ± 10.3	38.7 ± 10.6

Presented as mean ± standard deviation; BMI = body mass index; FFM = fat free mass; TBW = total body water

BMI, total body water, fat free mass and fat did not change significantly ($p>0.05$) in either group over the 12-week intervention (Table 7.3).

Table 7.4 – Primary and secondary outcome measures at baseline (t_0)

Presented as *mean ± standard deviation* (SD) and to two decimal places (*2dp*)

		RT1 (n=7)	**RT3 (n=10)**	**Total (n=17)**
Ultrasound measures at mid-VL point	VL ACSA (*cm^2*)	19.15 ± 3.15	18.24 ± 6.91	18.61 ± 5.55
	VL depth (*cm*)	2.54 ± 0.24	2.27 ± 0.38	2.38 ± 0.35
	Total muscle depth (*cm*)	4.03 ± 0.31	3.88 ± 0.60	3.95 ± 0.49
	Fat depth (*cm*)	1.27 ± 0.87	1.24 ± 0.68	1.25 ± 0.74
	VL pennation angle (*degrees*)	15.44 ± 2.35	16.83 ± 1.61	16.26 ± 2.01
	VL fascicle (fibre) length (*cm*)	3.35 ± 1.07	3.36 ± 1.52	3.36 ± 1.48
Isometric muscle strength	Knee extension peak force 45 (*Newtons*)	266.13 ± 126.33	343.86 ± 114.14	311.85 ± 121.93
	Leg press peak force (*Newtons*)	314.86 ± 161.08	217.25 ± 99.81	257.44 ± 133.36
Physical Function and Activity	Sit-to-stand 5 (*secs*)	12.29 ± 2.04	12.38 ± 2.04	12.34 ± 4.17
	Sit-to-stand 60 (*count*)	21.57 ± 5.91	25.30 ± 5.91	23.76 ± 6.73
	NSRI walk test (*secs*)	90.81 ± 19.55	79.82 ± 15.30	84.35 ± 17.49
	Physical Activity Recall (*kcal/kg/week*)	246.04 ± 11.17	255.13 ± 26.53	251.38 ± 21.54
Uraemic Symptoms	LUSS 1 (*number*)	6.71 ± 2.87	5.10 ± 2.87	5.77 ± 2.44
	LUSS 2 (*frequency*)	14.00 ± 8.98	13.10 ± 8.98	13.47 ± 7.80
	LUSS 3 (*intrusiveness*)	7.00 ± 5.94	6.50 ± 5.94	6.71 ± 4.82

7.3.2.1 Regional body composition:

7.3.2.1.1 Vastus Lateralis muscle and total thigh muscle depth

Figures 7.2 and 7.3 show that both VL-only and total thigh muscle depth at the mid-VL point increased significantly ($p<0.01$) over the 12-week intervention, irrespective of group allocation (no group difference at any point; VL depth: t_o 2.38 ± 0.35 cm, t_{12} 2.61 ± 0.41 cm, total thigh muscle depth: t_0 3.95 ± 0.49 cm, t_{12} 4.29 ± 0.70 cm).

Figure 7.2 - Ultrasound measures of VL depth at mid-VL site

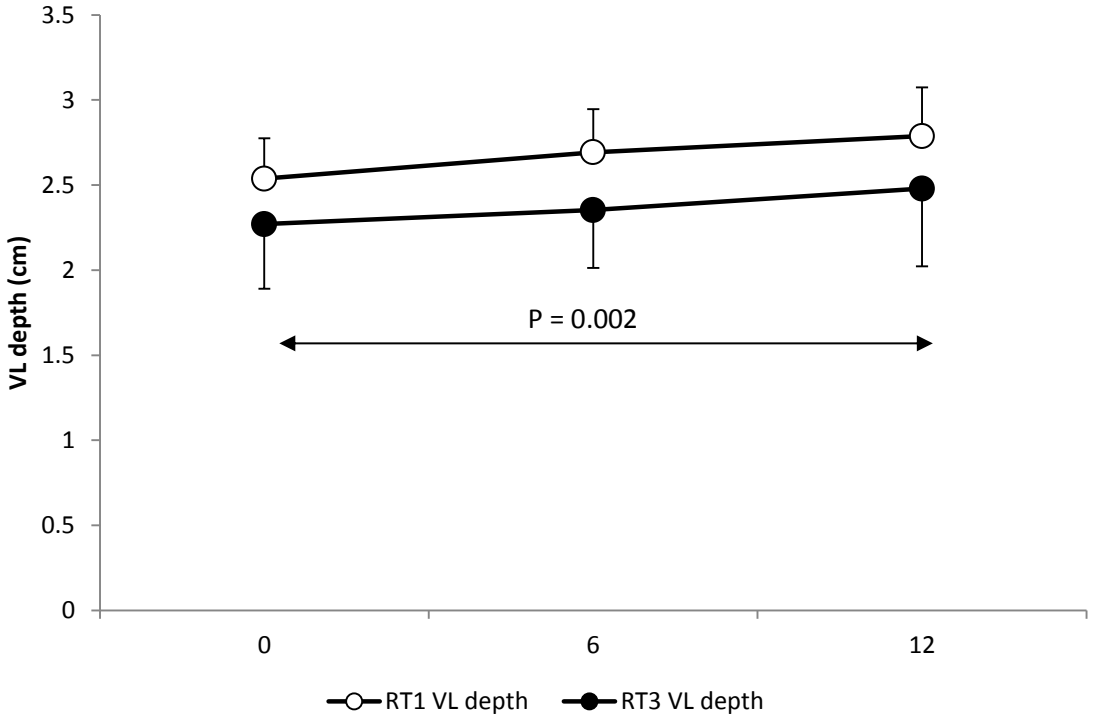
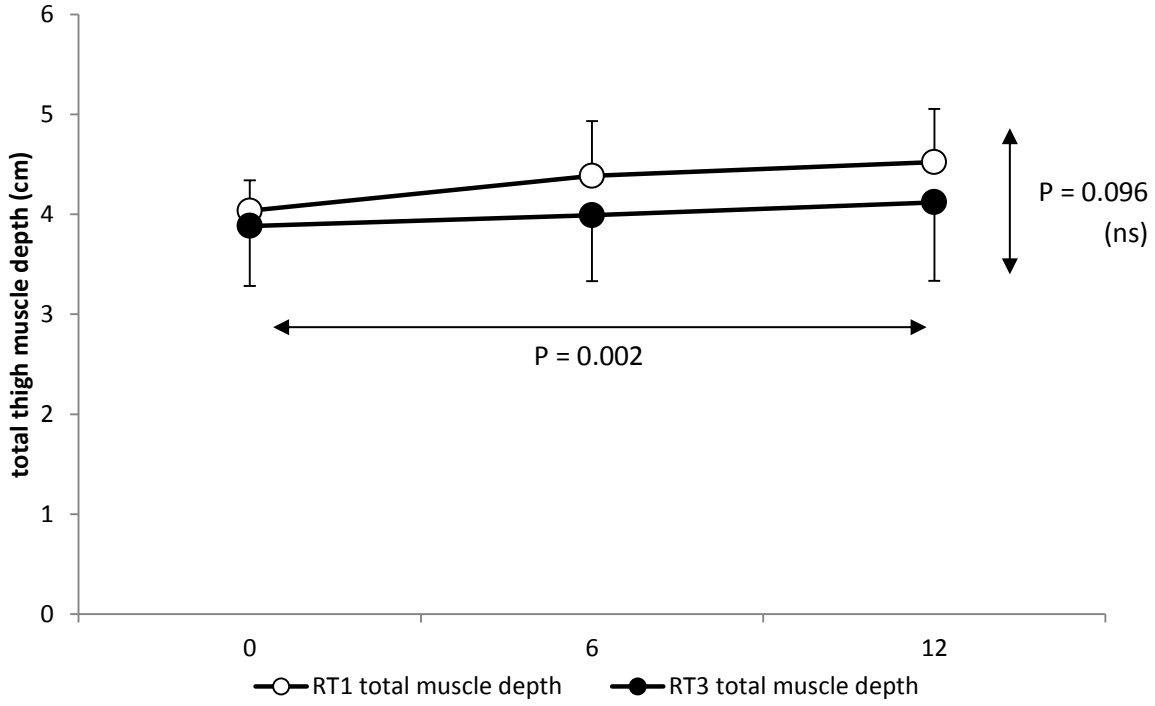


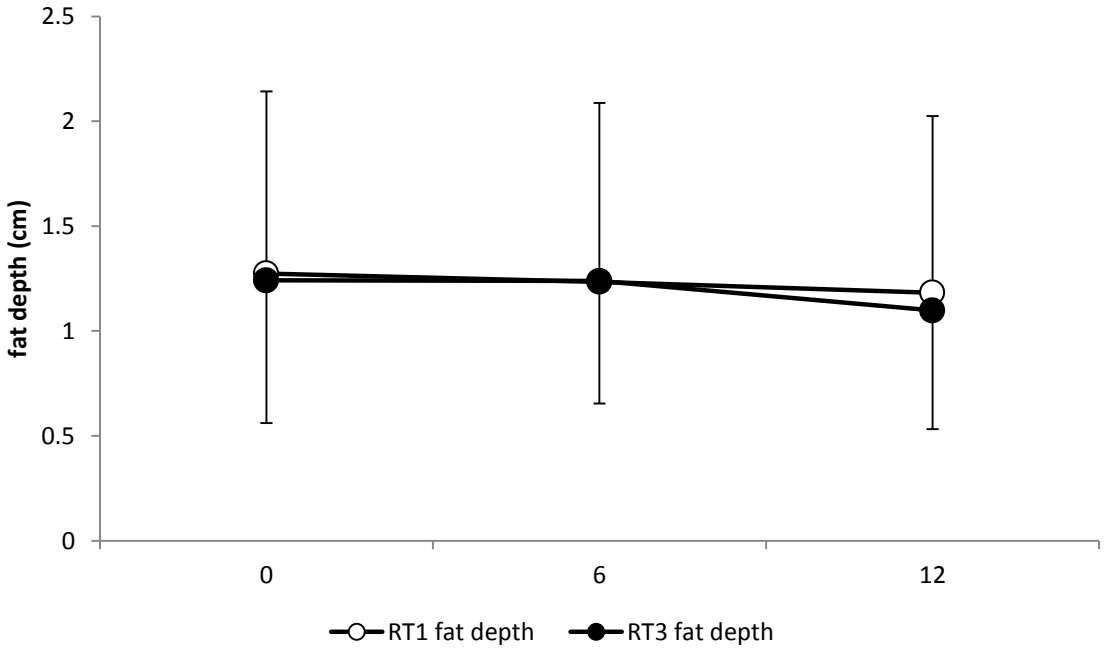
Figure 7.3 - Ultrasound measures of total thigh muscle depth at mid-VL site



7.3.2.1.2 Subcutaneous (mid-VL) Fat depth

Fat depth in the same location (mid—VL point) decreased over time, though not significantly (t_0 1.25 ± 0.74 cm, t_{12} 1.13 ± 0.67 cm, p=0.090). All changes remained relatively linear throughout (t_0 - t_{12}). There were no significant differences between groups at any point (Figure 7.4).

Figure 7.4 - Ultrasound measures of subcutaneous fat thickness/depth at mid-VL site

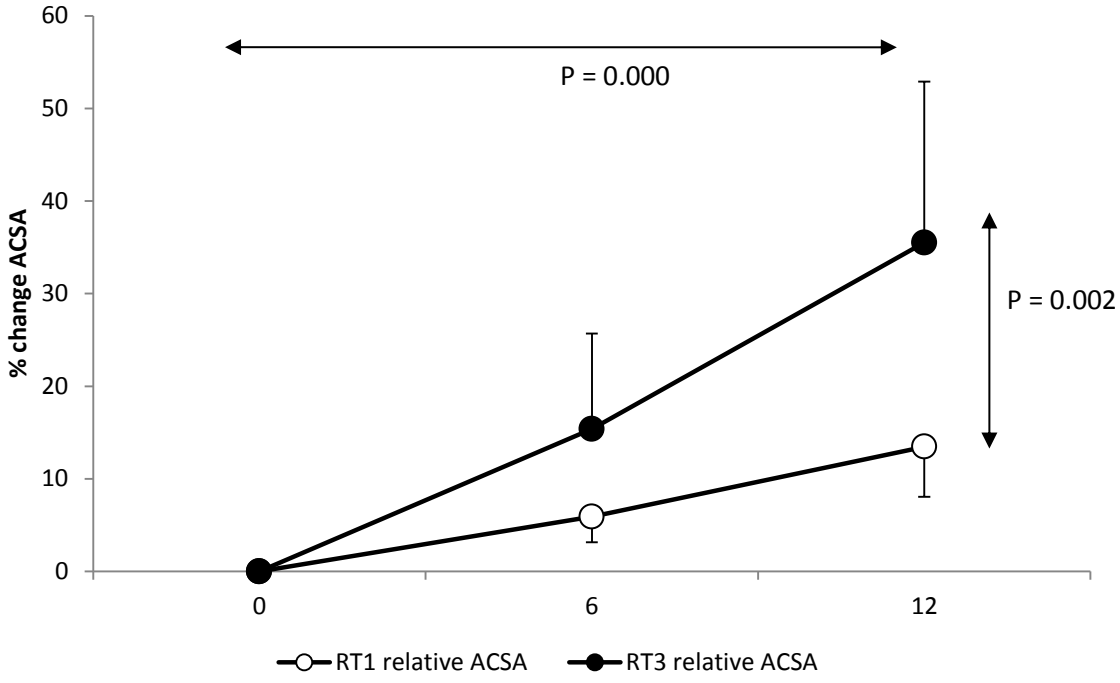


7.3.2.1.3 VL ACSA

VL ACSA had highly significant changes over time (12-weeks, p=0.000, Figure 7.5), and between groups (p=0.002, Figure 7.5); RT3 increased ACSA at mid-VL by an additional 3.1 cm^2 when compared to RT1 (RT3: t_0 18.24 ± 6.91 cm^2, t_{12} 23.88 ± 6.13 cm^2, RT1: t_0 19.15 ± 3.15 cm^2, t_{12} 21.67 ± 3.25 cm^2).

This equates to an increase of 30.8% in RT3 and 13.2% in RT1 over the 12-weeks (Figure 7.5).

Figure 7.5 - Relative (percentage) change over 12-weeks of VL ACSA at mid-VL site

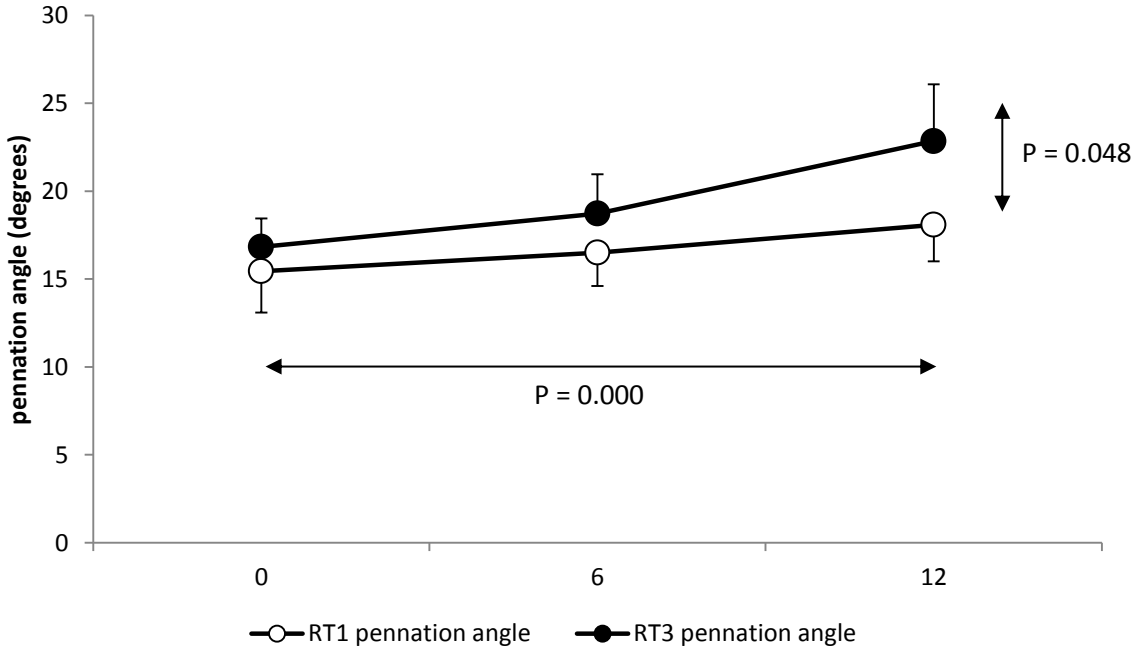


7.3.2.1.4 Muscle architecture

7.3.2.1.4.1 Pennation Angle (θ)

There was a significant interaction (group*time) in pennation angle over the 12-weeks (p=0.048). Figure 7.6 demonstrates an increase in both groups over time to t_{12} (t_0 16.26 ± 2.01 degrees, t_{12} 20.89 ± 3.65 degrees, p=0.000).

Figure 7.6 - Pennation angle within VL muscle at mid-VL site

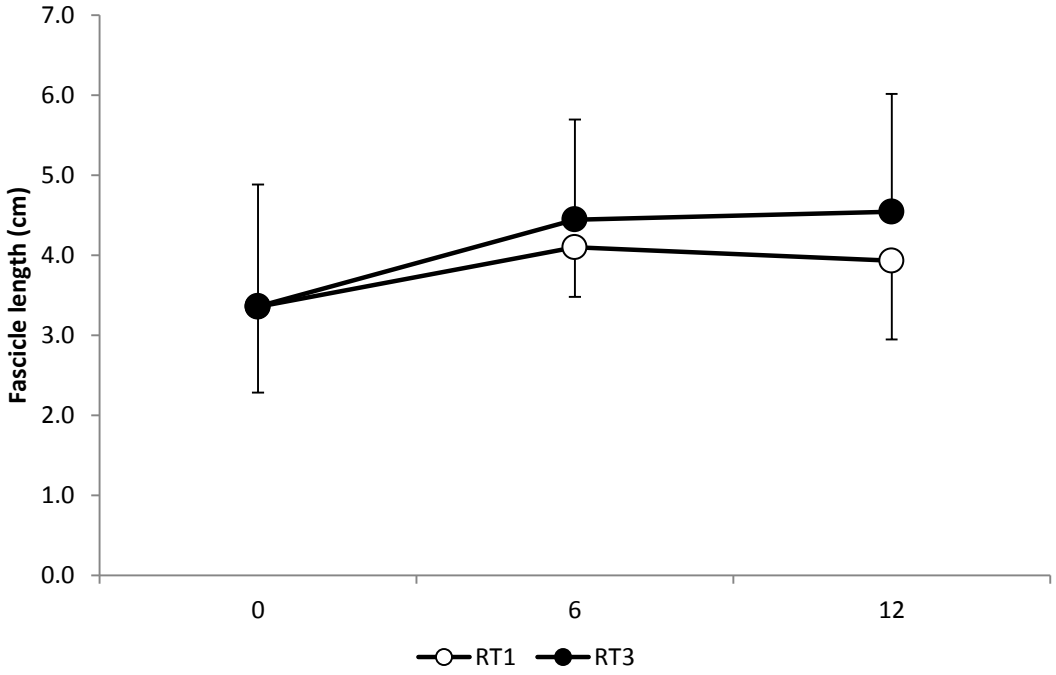


The overall change equates to an increased angle of 36.3% in RT3 by t_{12}; twice that seen in group RT1 (RT1 increased 17.5% over 12-weeks).

7.3.2.1.4.2 Fascicle (fibre) length

Fascicle length at the same location (mid—VL point) increased marginally over time, though this was not significant (t_0 3.36 ± 1.48 cm, t_6 4.28 ± 1.05, t_{12} 4.25 ± 1.36 cm, $p>0.05$). Despite the greater increase in RT3 than RT1 (Figure 7.7) there was also no significant group difference (or interaction) at any point ($p>0.05$).

Figure 7.7 - Calculated individual fascicle (fibre) length within the VL muscle at the mid-VL



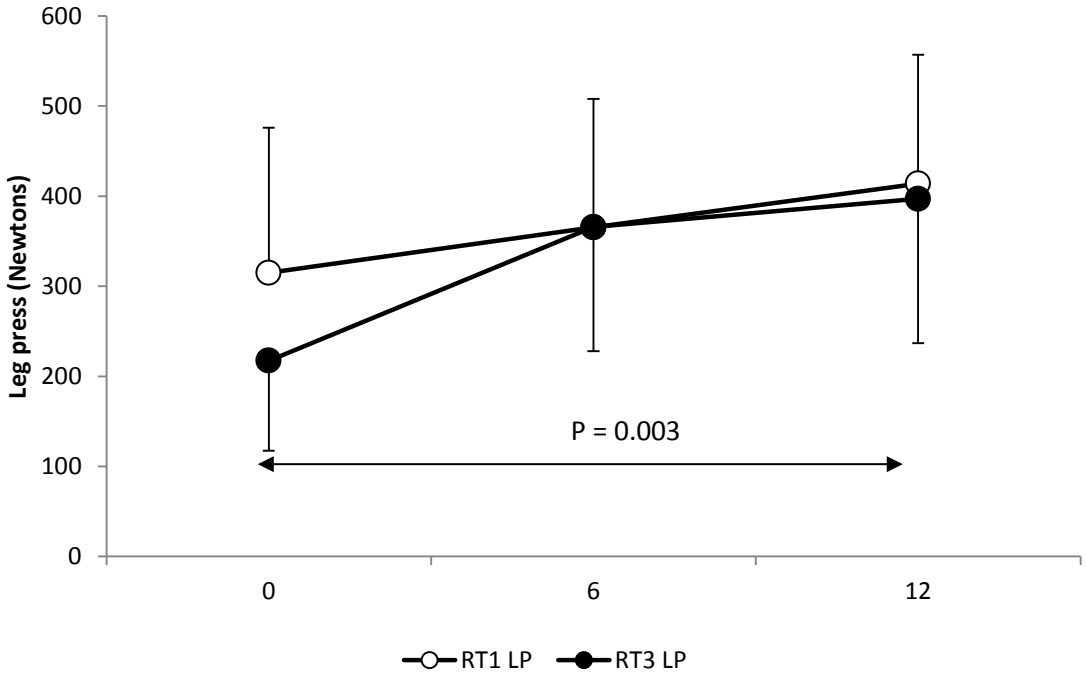
7.3.3 Neuromuscular performance (Strength measures)

7.3.3.1 Leg press and knee extension peak force

Both leg press (Figure 7.8) and knee extension peak isometric force (Figure 7.9) increased significantly over time ($p<0.01$) but with no significant group differences.

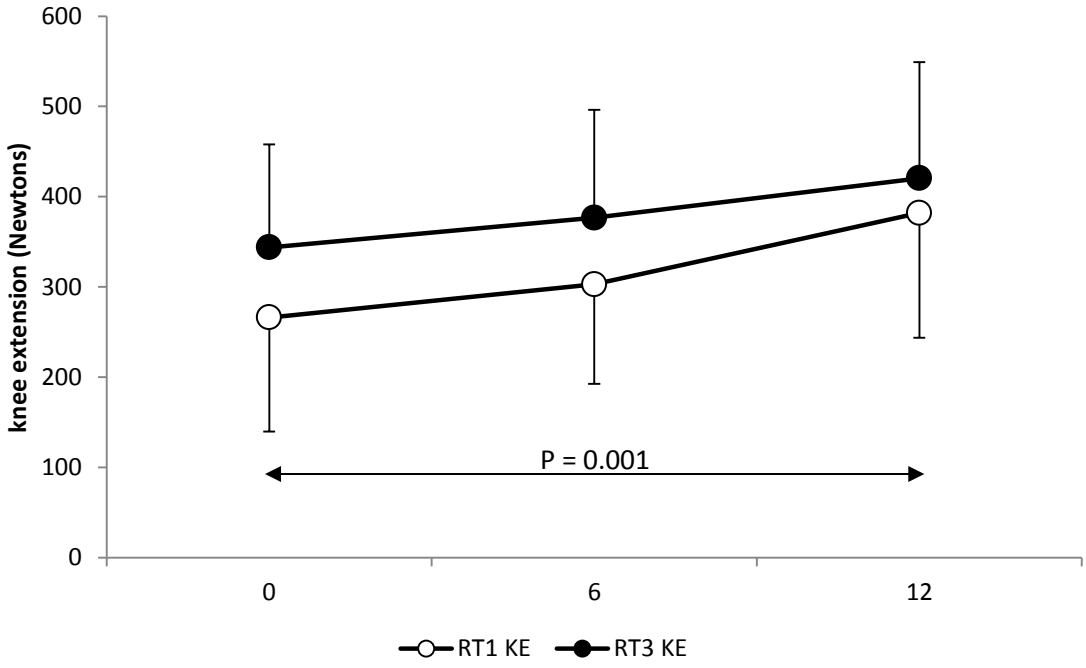
Leg press peak force increased by 57% over the 12-weeks (t_0 257.44 ± 133.36 N, t_{12} 403.89 ± 148.92 N, $p=0.003$), with the largest improvement of 42% by the mid-point.

Figure 7.8 - Leg press peak force (Newtons)



Despite the LP scores at baseline appearing to be 31% lower (~100N difference) in the RT3 group (Figure 7.8), this was not statistically significant ($p>0.05$).

Figure 7.9 - Knee extension peak force (Newtons)



Knee extension peak force increased by 30% over the 12-week intervention period (t_0 311.85 ± 121.93 N, t_{12} 404.59 ± 129.84 N, p=0.001), this time the larger improvement was in the second half of the intervention, as improvement only reached 11% by the mid-point.

Approximately two-thirds of the improvement in LP occurred in the first half of the intervention whereas KE almost two-thirds of the improvement took place in the second half of the intervention.

7.3.4 Functional Capacity

7.3.4.1 Sit-to-Stand

Figure 7.10 (STS5) shows no statistical differences between groups, but with significant improvements (p=0.000) over time. Most notable improvements occurred in the first six weeks (STS5: t_0 12.34 ± 4.17 secs, t_6 8.42 ± 2.26 secs, t_{12} 7.85 ± 1.86 secs) though both periods were significant.

Figure 7.10 - Improvements in STS5 over 12-weeks

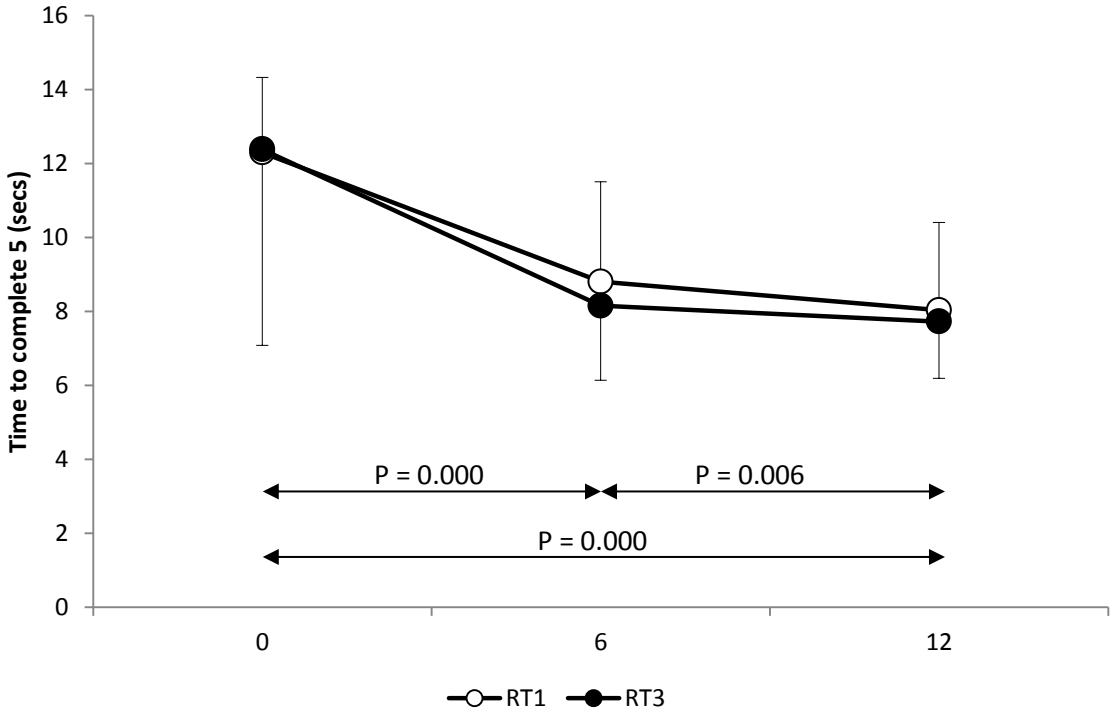
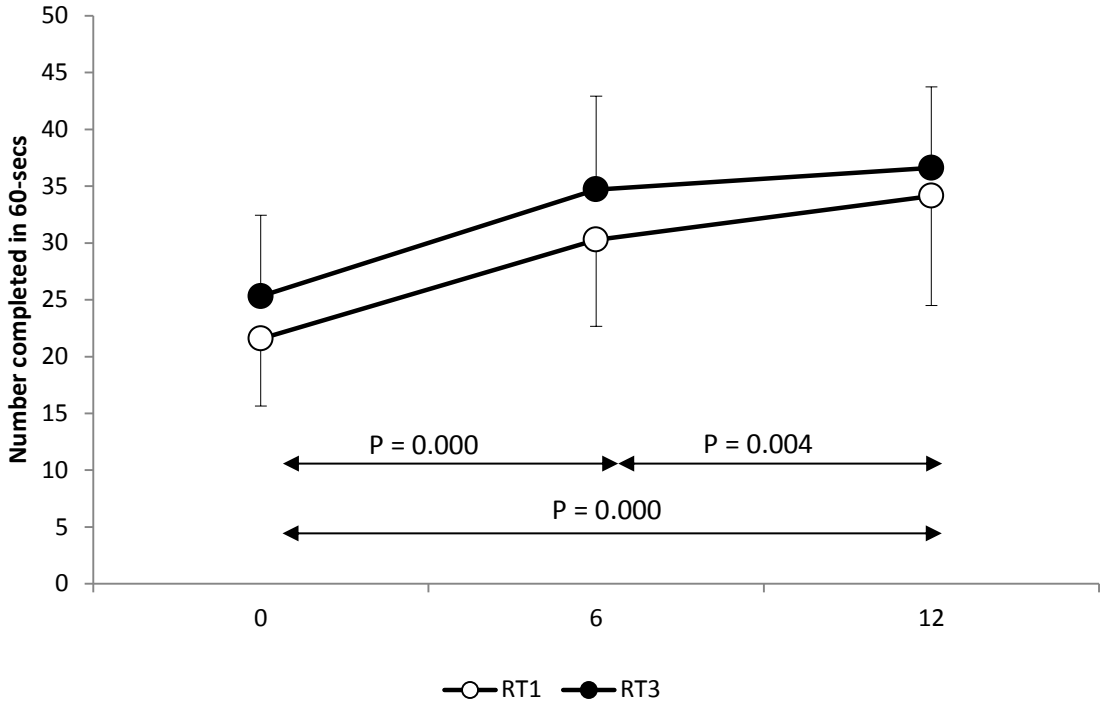


Figure 7.11 - Improvement in STS60 over 12-weeks



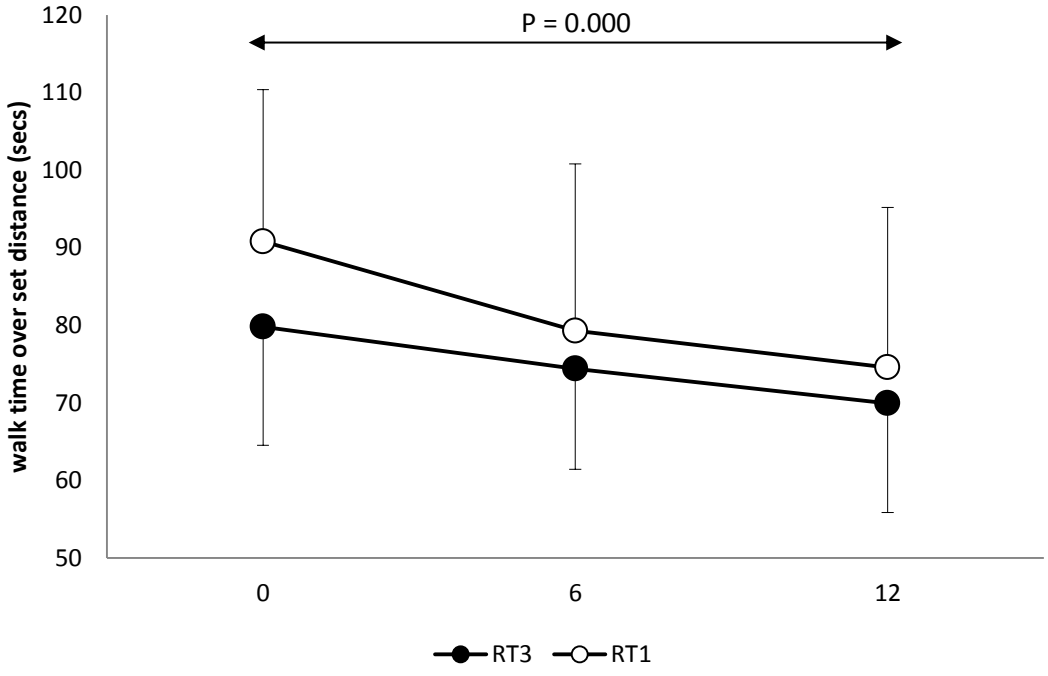
There were highly significant (p=0.000) improvements over the 12-week period, (STS60: t_0 23.76 ± 6.73, t_6 32.88 ± 8.05, t_{12} 35.59 ± 8.06), though more significant in the first 6-week (p=0.000) than the second 6-week period (p=0.004) again.

There were no group differences over the complete 12-weeks, but when analysed separately differences can be seen in the second six-week period, with significant differences between groups (p=0.015) from the mid-point (t_6) to the end (t_{12}) as group RT1 continued to improve at a greater rate (Figure 7.11). This is likely due to their slightly lower scores throughout.

7.3.4.2 NSRI Walk test

Figure 7.12 clearly shows that a significant (p=0.000) and relatively linear change over time occurred in both groups in the walk test, improving (reducing the time taken) by an average of 14.7 ± 9.1% in 12-weeks. There were no differences between groups.

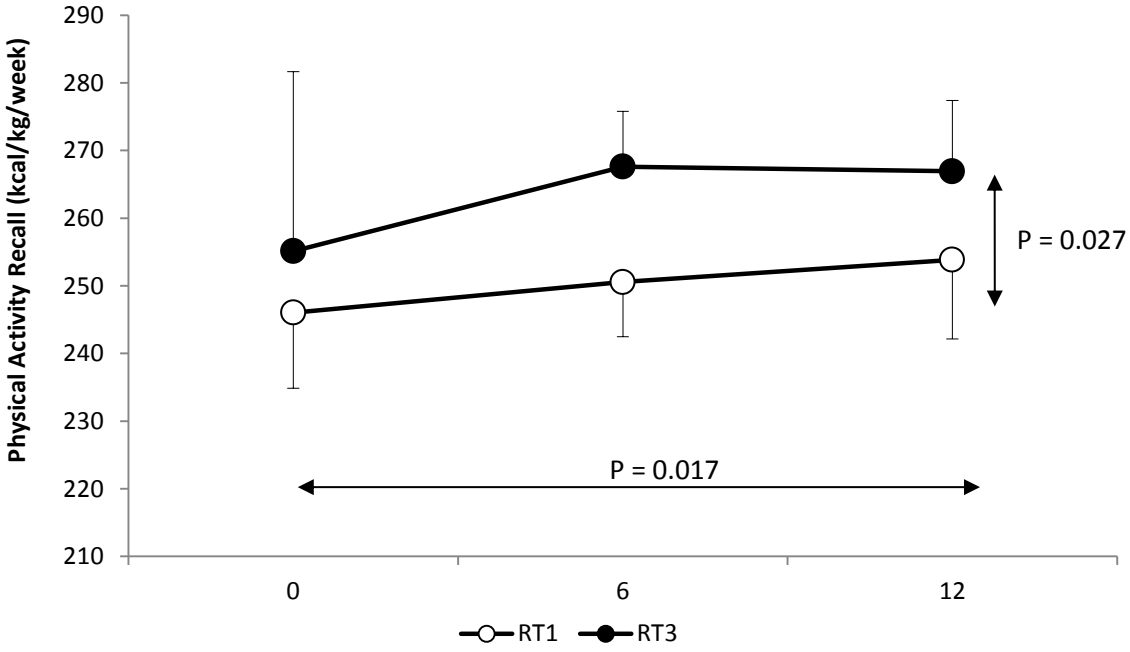
Figure 7.12 - Time to complete walk test (seconds)



7.3.4.3 Physical Activity Recall (PAR)

Figure 7.13 demonstrates a positive change (increased energy expended participating in physical activity each week, kcal/kg/week) in both groups over the time period (p=0.017, t_0: 251.38 ± 21.54 kcal/kg/week, t_6: 260.59 ± 11.71 kcal/kg/week, t_{12}: 261.54 ±12.55 kcal/kg/week).

Figure 7.13 - Self-reported PAR (kcal/kg/week)



Self-reported physical activity in group RT1 grew steadily throughout the intervention whereas RT3 showed larger increases from baseline to t_6 then plateaued (small decrease) to t_{12} (p=0.027). The standard deviation also decreased in RT3 between t_0 and t_{12} (Figure 7.13). The greater increase in the first six weeks in group RT3, and smaller standard deviation is likely due to the set additional supervised training sessions as part of the intervention.

7.3.5 Uraemic Symptoms (Leicester Uraemic Symptom Scores)

7.3.5.1 LUSS 1 (number), 2 (frequency), 3 (intrusiveness), and summative (total) score

Figure 7.14 shows the change in self-reported uraemic symptoms over the 12-week intervention period. No differences occurred between groups over the 12-week intervention as number (Figure 7.14a, LUSS1), frequency (Figure 7.14b, LUSS2) and intrusiveness (Figure 7.14c, LUSS3) of symptoms, and consequently total score (Figure 7.14d) fell significantly ($p<0.05$).

As with the functional tests this was most notable in the initial 6-week period, particularly the number (Figure 7.14a, LUSS1: t_0 5.8 ± 2.4, t_6 4.9 ± 2.3, t_{12} 4.6 ± 2.7, $p=0.006$) and frequency (Figure 7.14b, LUSS 2: t_0 13.5 ± 7.8, $t_6$9.8 ± 5.8, t_{12} 8.4 ± 5.5, $p=0.002$) of uraemic symptoms.

Significant reductions were also seen in the intrusiveness (Figure 7.14c, LUSS3) of uraemic symptoms (LUSS 3: t_0 6.7 ± 4.8, t_{12} 3.7 ± 2.7, $p=0.018$) and total LUSS score (Figure 7.14d, t_0 25.9 ± 13.9, t_{12} 16.7 ± 10.0, $p=0.002$) over the 12-weeks.

Figure 7.14a - LUSS1 (Number of symptoms; max score = 11)

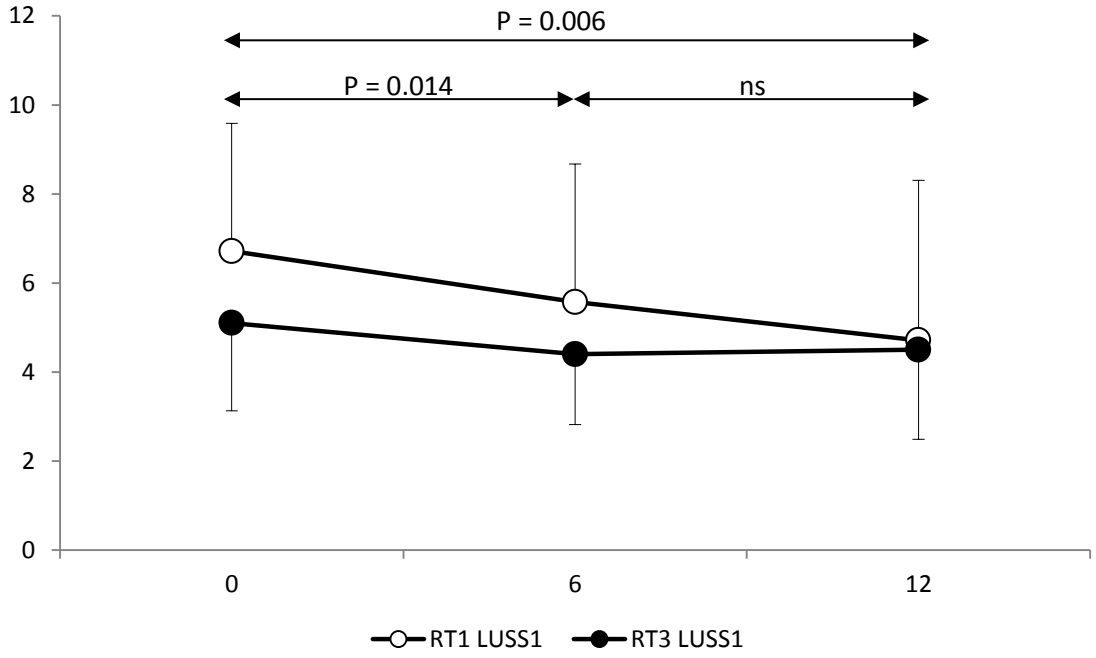


Figure 7.14b - LUSS2 (Frequency of symptoms; max score = 44)

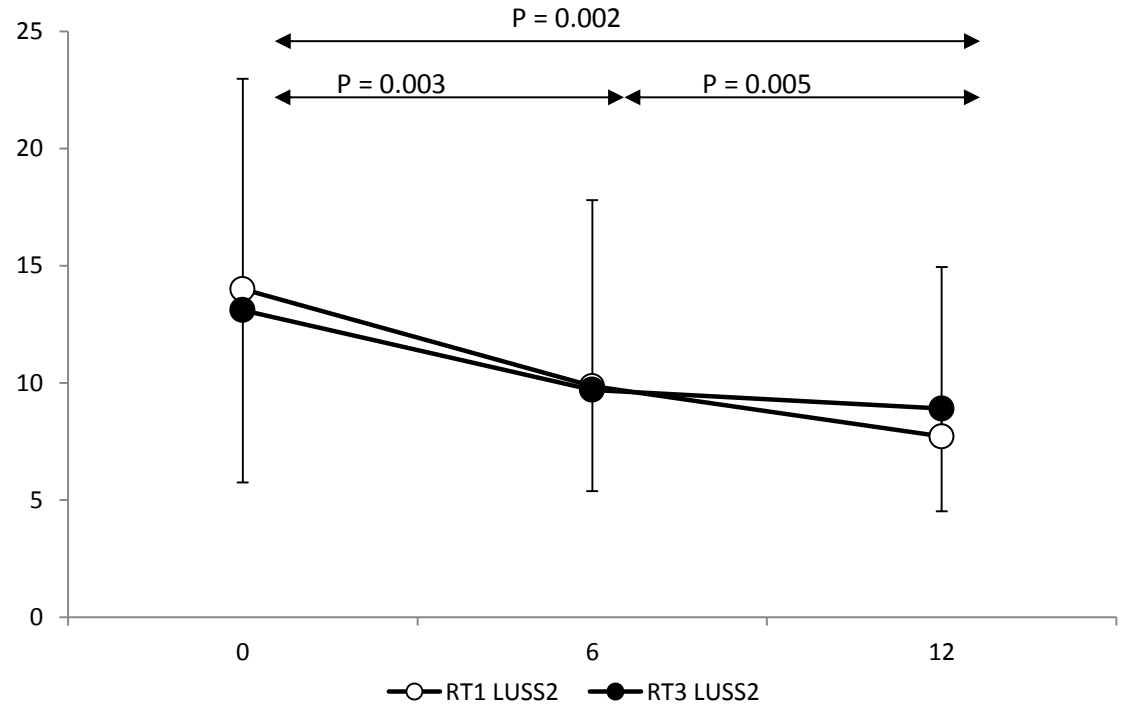


Figure 7.14c - LUSS3 (Intrusiveness of symptoms; max score = 44)

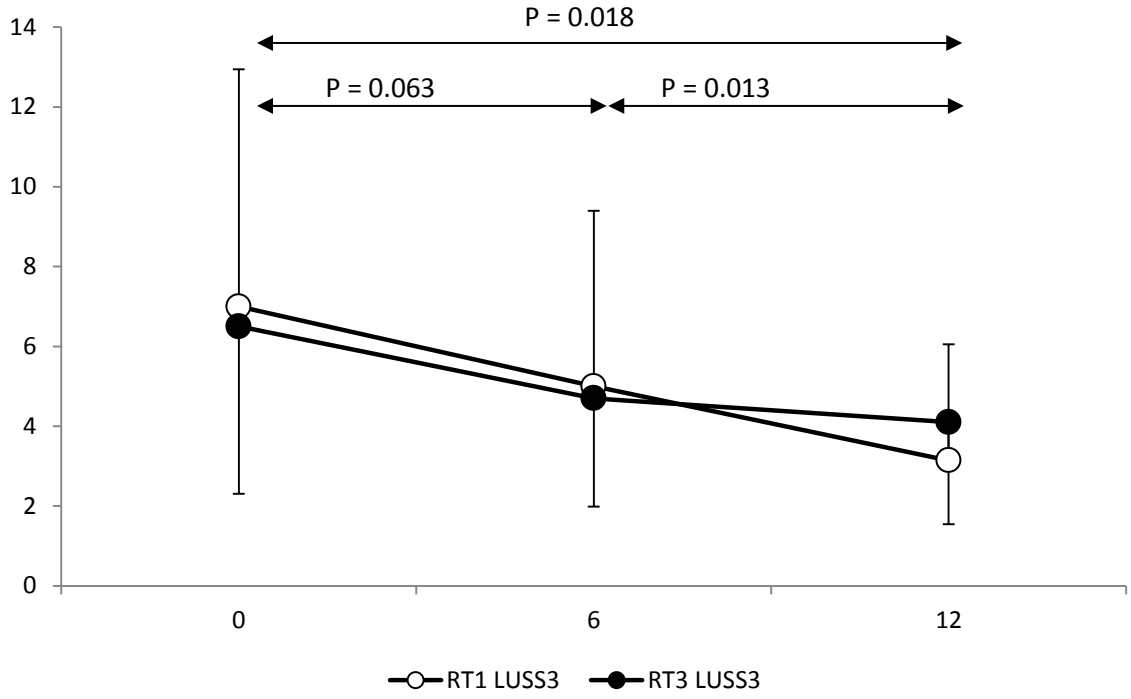
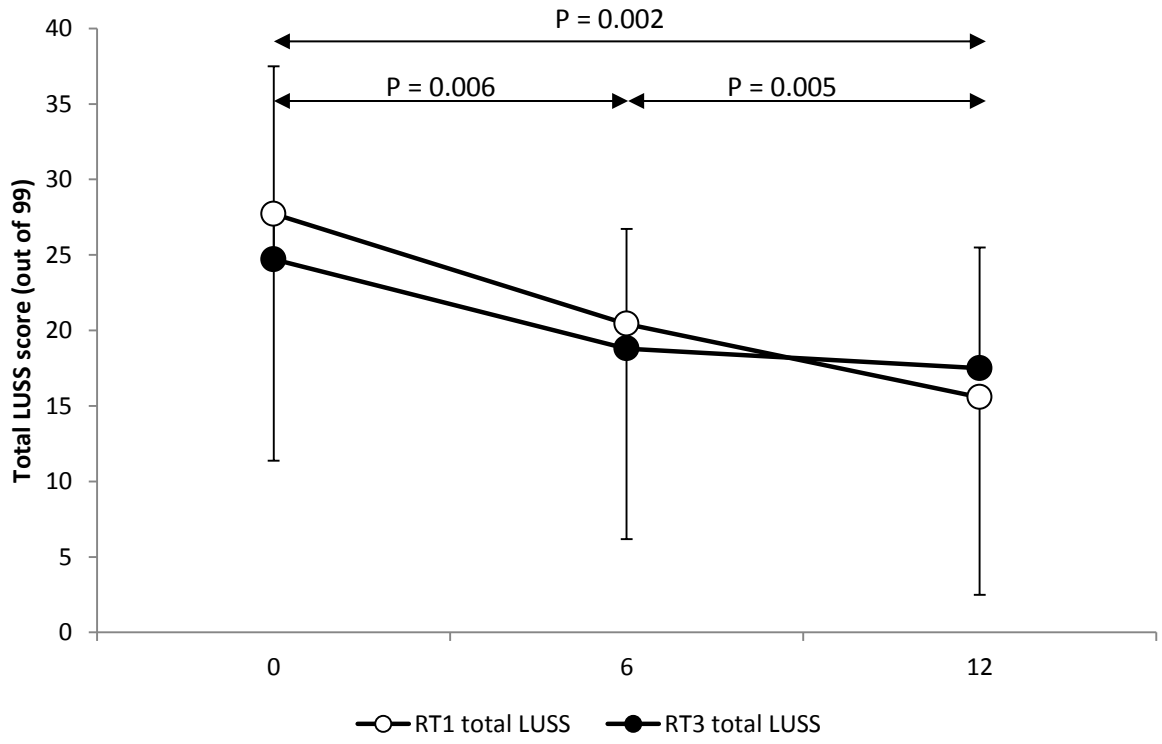


Figure 7.14d - Total score of LUSS (out of a possible 99; summative score)



7.4 Discussion

It was hypothesized that the effects of exposure to the intervention (resistance training programme) once per week (RT1) would be significantly different from those patients exposed three times per week (RT3). However, the results of the study show that there were no discernible (statistical) differences between the training groups in strength, function, and uraemic symptoms. The changes over time were consistently greatest in the first half of the intervention (t_0-t_6). In contrast, VL muscle size and architecture showed most notable changes from the mid-point onwards, with group differences becoming more pronounced as the intervention continued.

7.4.1 Whole and regional body composition

7.4.1.1 Subcutaneous (mid-VL) fat depth

The non-significant reduction, or no change, in subcutaneous fat depth at the mid-VL point (↓0.12cm, t_0 1.25 ± 0.74 cm, t_{12} 1.13 ± 0.67 cm) falls below the established MDC (0.22cm; Table 5.3). This was not unexpected as there were no significant or observable changes in overall fat mass (Table 7.3) and previous studies where the intervention is purely resistance training (with no cardiovascular element) have found similar responses (CKD HD, PEAK study, Cheema et al 2007).

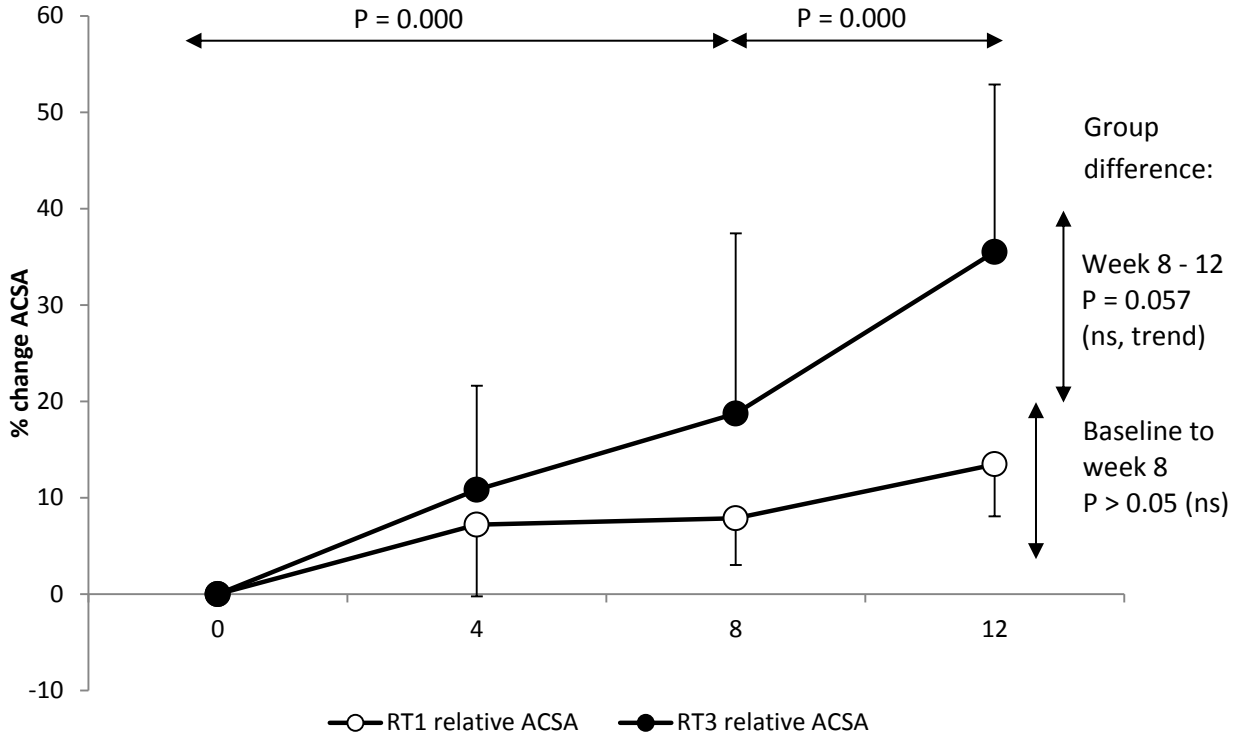
7.4.1.2 Mid-VL site muscle

7.4.1.2.1 VL ACSA

The actual (absolute) increase in VL ACSA in group RT1 after only twelve sessions (12-weeks; RT1t_{12} ↑2.51 ± 0.8 cm^2) showed similar improvements as group RT3 did after 18 sessions (six-weeks; RT3t_6 ↑2.56 ± 1.4 cm^2). The percentage (relative) change also indicates that the total increase in ACSA in RT1 (12 sessions; RT1t_{12} ↑13.2%) also occurred between 12 and 18 sessions (between t_4 and t_6) (RT3t_4

10.8%, RT3t_{12} 15.4%); a very similar improvement brought about over fewer sessions (but a longer period of time).

Figure 7.15 - Relative (percentage) VL ACSA measured every four weeks, showing significance over time from baseline (t_0) to t_8 (p=0.000), and the last four weeks (t_8 – t_{12}, p=0.000), and non-significant differences between groups from baseline (t_0) to t_8 (p>0.05, ns), and the last four weeks (t_8 – t_{12}; p=0.057, ns, trend)



Rate of change over 12 weeks (Figure 7.5, RT1: y=0.4108x, RT3: y=0.9165x) indicates more than twice the gradient in RT3, however this is likely due to the last four weeks (t_8 - t_{12}) when the rate of change was almost three times greater in RT3 than RT1 (fig 7.15, RT1: y=0.509x, RT3: y=1.3456x).

Muscle hypertrophy is unlikely to occur in the first four weeks of a resistance programme (Moritani & deVries 1979; Folland & Williams 2007) and this is seen as the group difference is visible only from t_4 (ACSA Fig 7.15) though it is not significant at this point ($p>0.05$). The delay in muscular adaptation for at least four weeks may be even more applicable to older/frail individuals whose hypertrophic adaptations are compromised compared to young/healthy adults (Welle et al 1996; Bickel et al 2011).

7.4.1.2.2 Muscle architecture

7.4.1.2.2.1 Pennation angle

Similar patterns are seen for pennation angle and ACSA measures; actual (absolute) increases in pennation angle in group RT1 after 12 sessions (12 weeks) are very similar to RT3 after a greater number of sessions (24 sessions, 8 weeks) but over a shorter time period ($RT1t_{12}$ 2.65 ± 1.2°, $RT3t_8$ 2.67 ± 2.2°). In terms of percentage (relative) change, this equates to RT1 at t_8 (11.72 ± 13.2%, 8 sessions) and RT3 at t_6 (11.37 ± 9.7%, 18 sessions). A larger cohort is needed to claim statistical significance at each time-point; however, the data (and graphical representation; Figure 7.16a-b) does indicate this strongly. Remodelling of muscle architecture has been shown to precede gains in muscle CSA (Seynnes et al 2007).

A larger pennation angle (angle at which fascicles attach to aponeuroses of the muscle) allows more contractile material to be accommodated along the tendon length, leading to a larger physiological cross-sectional area (PCSA) and greater force production by the muscle (change in pennation angle alone does not affect the anatomical cross-sectional area [ACSA] as greatly as it does PCSA).

The increased pennation angle is most notable from t_8 when RT3 continued at a significantly (p=0.009) greater rate of change to t_{12} (t_0 16.83 ± 1.61°, t_8 19.49 ± 3.11°, t_{12} 22.85 ± 3.24°) than RT1 (t_0 15.44 ± 2.35°, t_8 17.15 ± 2.75°, t_{12} 18.09 ± 2.08°), with no significant group differences between baseline and t_8 (Figures 7.16a-b).

Figure 7.16a - Vastus Lateralis pennation angle measured every four weeks, showing significance over time from baseline (t_0) to t_8, and the last four weeks (t_8 – t_{12}), and between groups from baseline (t_0) to t_8 (ns), and the last four weeks (t_8 – t_{12}; p=0.009)

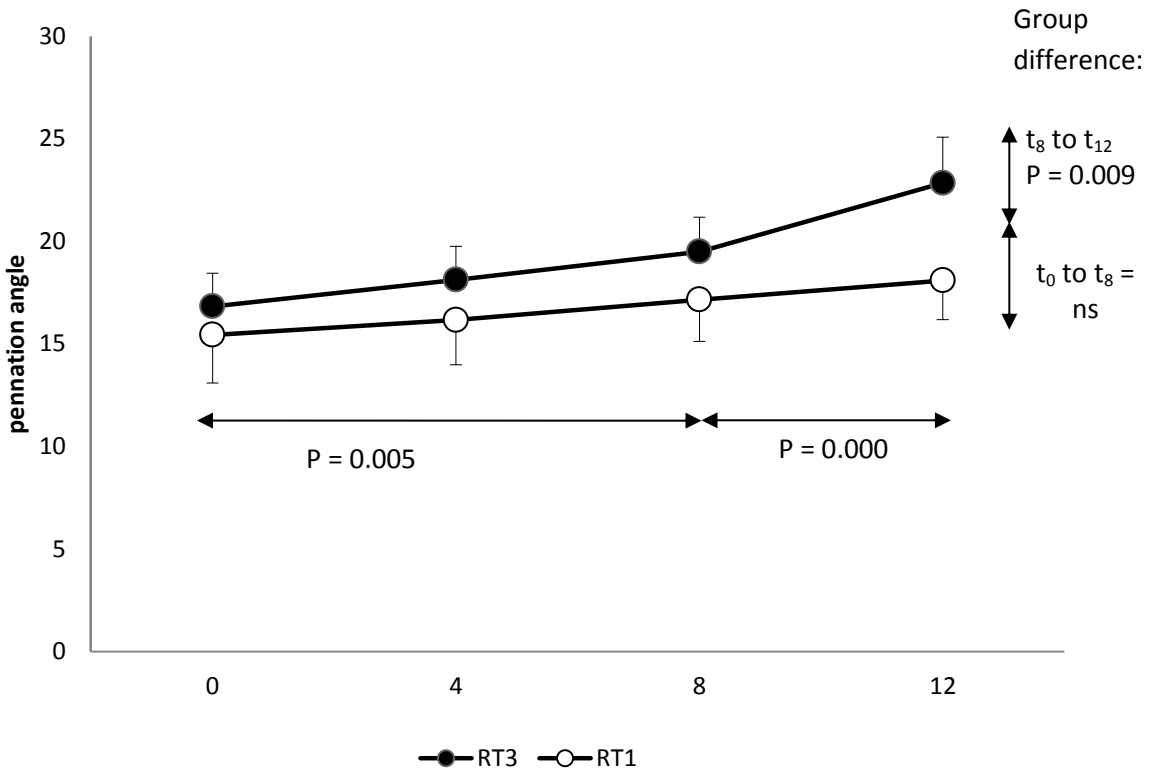
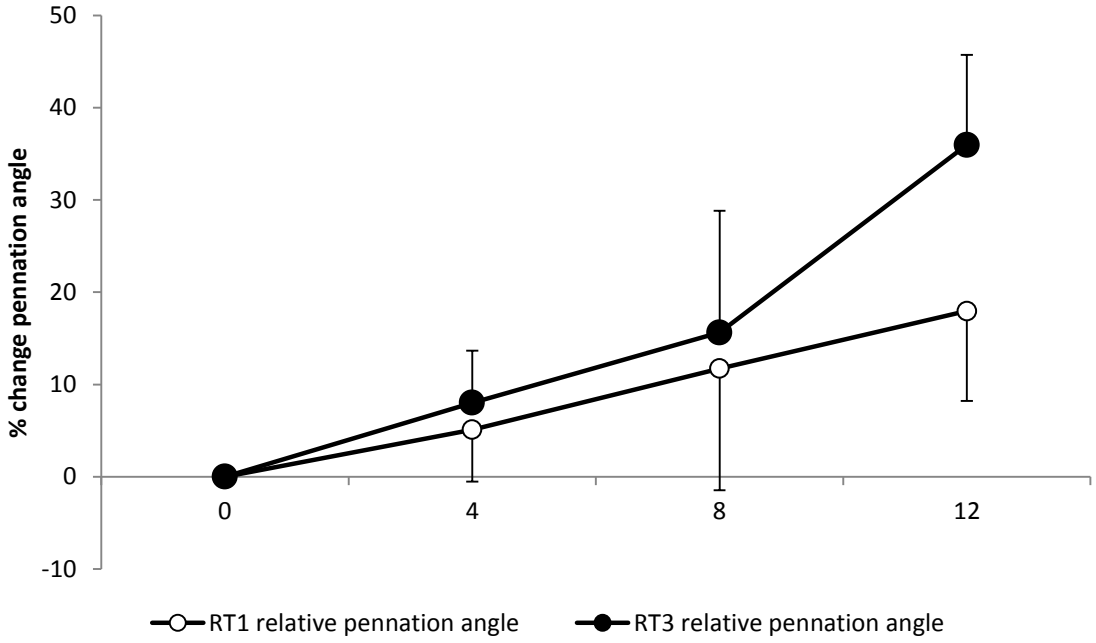


Figure 7.16b - Relative change in VL pennation angle from baseline every four weeks



The increase in pennation angle over 12-weeks for both groups was significant (RT1 17.5 ± 9.8%, RT3 36.3 ± 15.5%) and comparable to other studies (35.5%, Aagaard et al 2001; 35%, Reeves et al 2009). Studies that described smaller significant increases had less variety within the "lower body" resistance training intervention (5%, 9-weeks, leg extension exercise only, Erskine et al 2010) or a much shorter intervention period (7.7%, 35-days, Seynnes et al 2007) than the others.

7.4.1.2.2.2 Fascicle length

The results from this study showed no significant change in fibre length over the 12-week intervention or between groups. This is in agreement with a review of resistance training studies (Blazevich 2006) that reported increases in pennation angle and the physiological cross-sectional area (PCSA) but little or no changes in the length of the muscle fascicle (bundle of individual muscle fibres).

The lack of change in muscle fascicle length described by Blazevich et al (2006) and also seen here suggests that a major contribution to the larger VL ACSA (RT3 t_{12} 30.8%) was in fact the larger pennation angle (RT3 t_{12} 36.3%). Though to directly use this to approximate the PCSA of a pennate-fibre muscle, such as the vastus lateralis, may result in an underestimation of the PCSA true value; suggesting that it could be theorised that the PCSA would have grown by at least 30.8% (approximately one-third) with maximal force production increasing accordingly. This is in agreement with the strength results of this study (leg press peak force ↑57%, Figure 7.8, knee extension peak force ↑30%, Figure 7.9).

Vitally though, the differential group increase in size of both ACSA and pennation angle of the vastus lateralis muscle only became significant from week eight (t_8) onwards (Figures 7.15 - 7.16), suggesting it may take at least eight-weeks before the muscle is able to adapt more efficiently to the different training volumes.

7.4.2 Strength – Handgrip, Leg Press and Knee Extension Peak Force

RT3 handgrip strength was ~2.5kg greater than RT1 at baseline. This was not a significant group difference and lies below the minimally detectable change (MDC) for this measure calculated in the previous literature (3.4kg, CKD HD, Segura-Orti & Martinez-Olmos 2011; 4kg, diabetes, Alfonso-Rosa et al 2013; 5.1-5.2kg, cardiac rehab, Puthoff & Saskowski 2013).

It is possible that the gender proportions in each group may have driven the baseline differences observed in the leg press and handgrip results (RT1 43% female, RT3 60% female) as a larger percentage of females in one group would normally lower the average in strength tests, though this was not reflected in either the baseline handgrip (RT3>RT1) or knee extension (RT3>RT1) strength scores. Additionally, already within the first two-weeks, RT3 leg press peak force had increased the average maximal leg press from 217.25 ± 99.81 N to 274.03 ± 101.09 N, suggesting it was more likely a technical error that skewed the data. Therefore if we void the RT3t_0 and instead use RT3t_2 as a baseline point in group RT3 to account for this possible technical error, the overall improvement within the pooled data set (using t_2 as baseline in both groups) is still highly significant (37% increase from t_2 to t_{12}, p=0.002) by the final assessment point (t_2 295.00 ± 124.19 N, t_{12} 403.89 ± 148.92 N) with 24% improvement by the (t_6) mid-point (t_2 to t_6).

It is generally accepted that there is a delay before the onset of muscle hypertrophy and that the initial strength gain is mostly due to the intervention of neural factors (Seynnes et al 2007; Moritani & deVries 1979). Several investigators have reported a rapid increase in neural drive, during a maximal contraction, within a few weeks of strength training, demonstrated by an increase in integrated electro-myographic (EMG) activity (Narici et al 1989, Hakkinen et al 1996). The improvement in strength and function within the first half of the intervention can therefore be attributed to neural adaptation, which largely occurs within the first 6-weeks of a training programme (Enoka 1997; Blazevich 2006), and not the change in muscle size or structure.

The varying rate of improvement between the leg press and knees extension peak force tests (LP greater improvement in the first six weeks, KE greater proportion of

the improvement in the second six weeks), may be due to the greater contribution of the "hamstrings" in conjunction with the quadriceps in the leg press action compared to the quadriceps-isolating movement of the knee extension exercise. The usual hamstring to quadriceps ratio is 50-80% (where 100 percent would be equal strength; Rosene et al 2001), implying that the hamstrings are usually weaker than the quadriceps (with women having even lower ratios than men; Jaiyesimi & Jegede 2005), hence the greater rate of improvement initially in hamstring strength relative to the start point (represented in the leg press peak force).

7.4.3 Function – STS, NSRI walk test, PAR

The increase in the leg press peak force, especially in the first six-weeks of the intervention, is also reflected in the sit-to-stand test results which used the same movement pattern as employed in the resistance training programme. However, the sit-to-stand assessments do not isolate the muscles in use and instead must factor in other possible influences such as balance and speed of movement.

The more endurance-based sit-to-stand-60 highlighted greater improvement compared to the speed-assessed sit-to-stand-5 despite the movement pattern being identical. This is not in agreement with the conclusions of a recent systematic review of exercise in CKD (Heiwe & Jacobsen 2011) that found no improved muscular endurance (assessed by sit-to-stand-60) over a longer intervention (six-months, high intensity RT) though this analysis was based on only one study that used a resistance training intervention and assessed muscular endurance by STS60 (Segura-Orti et al 2009). The greater improvement of STS60 in this present study could be due to a number of reasons. The resistance training programme concentrated on repeated movement with a controlled and steady technique throughout the movement and not the speed. Simultaneously, the training may have affected the efficiency of oxygen uptake by the muscle, allowing the

participant to utilise the muscle more fully (Jang & Kim 2009). This could also offer some explanation of the dramatic improvements within the first 6-weeks in strength and function not attributed to either the change in muscle size (cross-sectional area), fibre alignment within the muscle (pennation angle), or neural adaptations, also noted in the walk test improvements to t_6.

The NSRI walk test has been validated and assessed as a proxy measure of VO_2peak in CKD patients (Mercer et al 1998). The reduced time recorded for both RT1 and RT3 groups suggests an improvement in this measure of maximal oxygen uptake, but once again with no differences between the group-frequency of training. Using the equation from a validation study;

[VO_2peak (ml/kg/min) = (-0.0767 x walk time in seconds) + (27.327)]

(Mercer et al 1998, p2024)

the improvement (change in walk time: ↓12.49secs, t_0 84.35 secs, t_{12} 71.86 secs) in VO_2peak over the 12-weeks is approximately 1.0 ml/kg/min, though this falls below the SEE (1.9 ml/kg/min, Mercer et al 1998). The larger increase in physical activity recall (PAR) in the first six weeks in group RT3 and smaller standard deviation is likely due to the set additional supervised training sessions as part of the intervention. The linear increase in activity over the complete 12-week intervention period would also suggest small increments in the participants' involvement in day-to-day activities which may also have contributed in a small way to the improved functional tests in both groups.

The dramatic changes of these functional tests potentially occurred earlier than the mid-point (t_6) but were not assessed as regularly as the body composition or strength measures.

7.4.4 Uraemic Symptoms

The reduction in each section of LUSS indicates an improvement in health-related quality of life as uraemic symptoms are reduced in number, frequency, intrusiveness, and total (summative) score. A cross-sectional study of HRQoL in CKD patients showed distinct differences in LUSS scores depending on the disease status (advanced CKD, moderate CKD, normal renal function; Pugh-Clarke et al 2006). The reduction as a result of this RT intervention represents a fall from advanced/moderate CKD levels to those more usually seen in patients with CKD with normal renal function (stages 1-2, GFR>60ml/min).

A six-month walking intervention (30-mins, five times/week, RPE 12-14) in pre-dialysis CKD 4 and 5, described a significant ($p<0.05$) reduction (improvement) in LUSS2 (frequency of symptoms), LUSS3 (intrusiveness of symptoms), and total score in the Leicester Uraemic Symptom Score but no change in the reported number (LUSS1) of symptoms (Kosmadakis et al 2012). This clearly shows the benefit of an exercise regime, as their control group (no walking exercise) demonstrated small (non-significant) increases or no change in all four areas (a worsening of symptoms in non-exercisers). However, the present study using resistance training for just 12-weeks, brought about significant improvements ($p<0.05$) in LUSS3 (intrusiveness) and highly significant improvements ($p<0.01$) in all other measures of uraemic symptoms (LUSS1, number; LUSS2, frequency; and total) with fewer training sessions (once or thrice per week) than the walking intervention (five times per week, Kosmadakis et al 2012).

The increased benefit of RT over walking in ameliorating the perceived number, frequency, and intrusiveness of uraemic symptoms will have been most noticeable in “loss of muscular strength or power” as significant strength gains were made across the intervention. The participants here reported a reduction on average of

slightly over one symptom (LUSS1, number, t_0 5.8 ± 2.4, t_{12} 4.6 ± 2.7), so others could be directly influenced by the RT intervention, including “restless legs, muscle spasm or stiffness, and pain in joints”.

This strongly indicates that resistance training in non-dialysis patients can lessen, and almost normalise, the day-to-day symptoms experienced by NDD, moderate CKD patients. Significant improvements were noticed within the first six-weeks in both training groups, and continued almost linearly through to the conclusion of the intervention (Figures 7.14a-d). Whether some of these improvements can be maintained following the cessation of exercise remains to be seen, or if the benefits would continue to progress at the same rate if the regimen was continued indefinitely.

7.4.5 Training Frequency/Volume

In young, healthy individuals a dose-response relationship between exercise frequency/volume and strength has been identified where increased volume leads to increased strength and muscle mass (Rhea et al 2003). Despite this, long-term resistance training of healthy untrained older adults where three different frequencies were implemented (once, twice, or three times per week) showed no group differences in muscle or strength gains after 24-weeks (Taaffe et al 1999). Shorter studies have replicated these findings, also showing no additional benefit with more frequent training (three times per week compared to only twice per week for 6-weeks, Candow & Burke 2007; three times or four times with split loads for 8-weeks, Benton et al 2011; two or three times per week for 8-weeks, torso strength, Murlasits et al 2012).

It has been suggested that for individuals that are deconditioned - such as those with chronic illness, the frail, or elderly - a training threshold may exist. That is, for initial training adaptations amongst the most deconditioned, when a threshold-stimulus is met, further increases in volume load or frequency may not result in greater gains in strength (Benton et al 2011). The results of this study reflect this proposition, as the significant group differences noted in body composition and structure did not occur in the initial stages and it was only with prolonged exposure (over eight-weeks) that they became apparent.

7.5 Study Strengths and Limitations

7.5.1 Limitations

The small study size (n=17) is limiting in the analysis as larger numbers may have increased the power (improved the significance) either between groups or over time as some indications of "trends" can be seen here in these results. The large variability in some of the baseline characteristics (e.g. age, weight, serum creatinine, Table 7.1), in conjunction with the small sample size, may account in part for the lack of statistically significant results later in the intervention.

Also, the relatively short duration of the intervention (12-weeks) is potentially limiting as group differences only began to appear later in the intervention. A continued programme of training beyond 12-weeks may have further highlighted the group differences in muscle size and structure, and may have developed differences between groups over time in functional and clinical outcome measures with a lengthier intervention.

Lastly, the lack of a true control group could be deemed a potential study limitation. However, the upper body verification/control data allowed us to observe the untrained muscle groups as the surrogate control for the training programme.

7.5.2 Research design strengths of the Study

Assessment of upper body strength and size clearly show that the untrained areas were unaffected (Table 7.2), allowing us to infer that any adaptations in the trained (lower body) can be attributed to the intervention.

In addition, each of the documented significant changes observed over the 12-week intervention were greater than the established error/ smallest detectable difference/ minimal detectable change. For instance, VL muscle depth increased by 0.23cm and total thigh muscle depth increased by 0.34cm (VL muscle thickness MDC 0.14cm, total muscle thickness MDC 0.19cm; Table 5.3).

This was also the case for the functional measures; NSRI walk time fell by 14.7% (SEE 11%, Mercer et al 1998), STS5 improved (decreased) by 4.49 seconds (minimal detectable change 1.7secs, COPD, Jones et al 2013; 2.5secs, older females, Goldberg et al 2012; 3.12sec, cardiac rehab, Puthoff & Saskowski 2013) and STS60 increased by 11.83 repetitions (MDC 4-repetitions, HD CKD, Segura-Orti & Martinez-Olmos 2011).

7.5.3 Relevance to CKD patient population

These results are very relevant to a broader population of CKD3 patients as this sample is similar to participant samples used in other studies (age, weight, BMI), despite group RT1 being slightly younger (53 years old) than RT3 (60 years old).

Body weight is also comparable; other studies have shown gender differences of approximately 10kg (women ~60kg, men ~70kg; Bellizzi et al 2006) and following drop-out in this study - group RT1 had lost 3 women - resulting in the mean weight of RT1 being greater (predominantly male) than RT3 at baseline.

7.6 Clinical Implications

Results of this study clearly show that for larger gains in ACSA and pennation angle of a resistance trained muscle, three sessions per week is better than one session per week. However, this was not reflected in the strength, function, or clinical tests. Therefore, implementing a programme of resistance training for those diagnosed with Chronic Kidney Disease early on is feasible and would be beneficial to those participating in terms of a reduction in uraemic symptoms as well as improved strength and function. For all outcome measures assessed in this study, the difference between training once or three times per week was statistically insignificant (over the first eight-weeks), suggesting that resistance training just once per week is adequate to bring about improvements relevant to the clinical population; delaying both the transition to dialysis and a possible diagnosis of frailty. Interventions should also be at least eight weeks in duration to overcome the apparent training threshold or adaptation limitation prior to this point.

7.7 Conclusions

Resistance training is feasible, practical, and effective in CKD3 patients.

Despite the group differences seen in the physiological adaptations in the measured VL muscle whether training once or three times per week, the functional and clinical response was similar, which is statistically significant and clinically beneficial in this population.

Resistance training once per week may therefore be an effective introduction or pre-habilitation programme for more elderly and deconditioned patients where improved strength, function, and health-related quality of life (through reduced uraemic symptoms) are the main objectives.

7.8 Further Research

Whether the gains in muscle size, strength, function, and reduction in uraemic symptoms, were maintained after the intervention was not examined and this limits our understanding of the long-term effects of the intervention in this study. Long-term follow-up comparing the group-frequency and usual care (or those unable to participate in the RT programme) could provide further information about whether a resistance training programme/intervention of this nature can bring about a delay before it become medically necessary to initiate dialysis.

Further research can to be done into prolonging the intervention to examine whether training once or thrice per week over a longer period brings about continued or greater improvements or whether a threshold is reached. Additionally, measuring changes in glucose and insulin sensitivity following the resistance training intervention would be of interest as diabetes is now the commonest cause of end stage renal disease (Collins et al 2005; Cheema et al 2007).

The state of inflammation (analysis of inflammatory markers) throughout the intervention period could also be of interest as this is also a major manifestation of CKD.

CHAPTER 8 – General Discussion

8.1 Introduction

This thesis set out to make an original contribution to knowledge in relation to methods of assessing muscle size and architecture in the Chronic Kidney Disease and End-stage Renal Disease population and to assess the ability to improve these muscle measurements by implementing an anabolic intervention (resistance exercise training) in the non-dialysis dependent CKD population.

As outlined in the introduction (Chapter 1), accurate measurement is vital to gain a deeper understanding of the relationship between the general atrophy observed in CKD patients both in early stages and once dialysis has been initiated, and the functional limitations that become instigators of frailty and reduced independence in this group.

The purpose of this final chapter is to consider and synthesize the findings from the four study chapters in greater depth and to evaluate these findings in the context of the existing literature. This chapter will also consider the limitations of the studies and discuss the implications for investigators and policy makers regarding measurement of total and regional body composition and the implementation of resistance exercise training as an anabolic therapy in CKD patients. Table 8.1 summarizes the research questions and key findings of this thesis.

Table 8.1 – Key findings of the thesis

Research question/ study	**Key findings of study**
Are there statistically significant differences between early-stage CKD and end-stage CKD in terms of body composition, strength and function? **(*Chapter 4*)**	• There is a statistical difference between CKD3 and CKD5 (CKD5 faring worse) in - • clinical measures (Hb and Albumin, $p<0.01$) • body composition (anthropometry $p<0.01$) • strength (handgrip and KEPF45 $p<0.05$) • function (STS5 $p<0.05$, STS60 ns, weekly PAR $p<0.01$) • uraemic symptom reporting ($p<0.01$)
Are current methods of assessment of body composition sufficiently discriminatory to track an individual's change over time, or from an intervention, using repeated measures, in CKD? **(*Chapter 4*)**	• SGA, BMI, body weight, %body fat are not precise enough to distinguish between the two stages. • Anthropometrical measures are sufficiently sensitive to distinguish different stages of the disease. • Circumference/girth measures (anthropometry) cannot distinguish between muscle and fat.
Is Ultrasound a valid form of measurement of regional body composition in CKD, when compared to a gold standard tool such as MRI? **(*Chapter 5*)**	• 2-D B-mode ultrasound is valid compared to MRI in measures of fat and muscle at the mid-VL site in CKD. • ICCs: VL ACSA 0.96, VL thickness 0.99, fat thickness 0.98 • Typical error: VL ACSA 0.61 cm^2 (2.6%), VL thickness 0.04 cm (1.8%), fat thickness 0.05 cm (6.0%)
Is Ultrasound reliable for use in the CKD population for repeated measures of regional body composition? **(*Chapter 5*)**	• 2-D B-mode US is reliable in repeated measures (by a single assessor) of fat and muscle at mid-VL. • ICCs: VL thickness 0.98, total muscle thickness 0.97, fat thickness 0.99 • MDC: VL thickness 0.14 cm, total muscle thickness 0.19cm, fat thickness 0.22 cm

Research question/ study	Key findings of study
Are accurate measures of muscle mass and muscle architecture by US related/correlated with functional and neuromuscular (strength) performance measures in early-stage CKD? **(*Chapter 6*)**	• Site specific body composition measures by US were highly correlated ($p<0.01$) to • Anthropometry (VL depth r=0.38-0.44, total muscle depth r=0.50-0.53, fat depth r=0.41-0.67) • Strength (VL ACSA r=0.35-0.45, fat thickness (-ve) 0.49-0.67) • Function (pennation angle r=0.45, fat thickness (-ve) 0.42-0.44)
Are any of the measurements used to assess body composition, frailty, and malnutrition in CKD patients related/correlated with patient-reported uraemic symptoms? **(*Chapter 6*)**	• Uraemic symptoms (frequency and intrusiveness) are highly correlated ($p<0.01$) to • VL muscle pennation angle (r= (-ve) 0.42-0.51) • anthropometry (MTC, MAC, r=0.35-0.40) • function (STS5 r=0.39-0.46, STS60 r= (-ve) 0.49-0.52, NSRI walk r=0.35-0.40)
Is there a greater difference in muscle size and/or architecture (at the mid-VL site) brought about a greater frequency of a 12-week resistance training intervention; three times per week compared to once per week? **(*Chapter 7*)**	• VL thickness: ($p<0.01$) improvement (increase) over time, ns between groups (RT3=RT1) • Total muscle thickness: ($p<0.01$) improvement (increase) over time, ns between groups (RT3=RT1) • Fat thickness: ns change over time, ns between groups (RT3=RT1) • VL ACSA: ($p<0.01$) improvement (increase) over time, ($p<0.01$) between groups (RT3>RT1) • Pennation angle: ($p<0.01$) improvement (increase) over time, ($p<0.05$) between groups (RT3>RT1) • Fascicle length: ns change over time, ns between groups (RT3=RT1)

Research question/ study	Key findings of study
Does a 12-week resistance training intervention bring about change in objectively measured strength and function, and patient-reported (subjective) uraemic symptoms? Does the frequency of the intervention affect this? **(*Chapter 7*)**	• LPPF45: ($p<0.01$) improvement (increase) over time, ns between groups (RT3=RT1) • KEPF45: ($p<0.01$)improvement (increase) over time, ns between groups (RT3=RT1) • STS5: ($p<0.01$) improvement (reduction) over time, ns between groups (RT3=RT1) • STS60: ($p<0.01$) improvement (increase) over time, ns between groups (RT3=RT1) • NSRI walk: ($p<0.01$) improvement (reduction) over time, ns between groups (RT3=RT1) • PAR: ($p<0.05$) improvement (increase) over time, ($p<0.05$) between groups (RT3>RT1) • LUSS1 (number): ($p<0.01$) improvement (reduction) over time, ns between groups (RT3=RT1) • LUSS 2 (frequency): ($p<0.01$) improvement (reduction) over time, ns between groups (RT3=RT1) • LUSS 3 (intrusiveness): ($p<0.01$) improvement (reduction) over time, ns between groups (RT3=RT1) • Total LUSS score: ($p<0.01$) improvement (reduction) over time, ns between groups (RT3=RT1)

8.2 Discussion of key findings

Table 8.1 summarises the key findings in each study, in response to the research questions and aims set out in the introduction (Chapter 1) and literature review (Chapter 2).

8.2.1 Using 2-D B-mode Ultrasound for body composition assessment

The key findings table (Table 8.1) shows that 2-D B-mode US is a valid method for assessing muscle and fat depth (thickness) at the mid-VL site when compared to a gold standard measurement technique (MRI) in the CKD population. The intra-rater reliability of all measurements was very high, showing excellent reproducibility at the mid-VL site.

Ultrasound (2-D B-mode) is valid and reliable method of body composition measurement to evaluate site-specific fat and muscle mass. US also allows measurement of muscle architecture (the muscle fibre arrangement within the muscle) which is not possible with other forms of portable/near bed-side assessment equipment (MAC, MTC, skinfold, BIA, muscle biopsy). Therefore utilising ultrasound to assess regional body composition provides an additional layer of information for researchers to assess the effectiveness of an intervention, or to track an individual over the course of the disease progression; possibly even providing objective, quantifiable, and accurate feedback to the patient regarding the need to intervene, or demonstrate progress (whether positive or negative).

Using US to assess muscle and fat depths at specific sites - such as the mid-VL used throughout the studies within this thesis - allows increased accuracy and specificity in the measurement of the different tissues. Some intervention studies have compared US to a “gold standard” for assessing muscular size adaptation (DEXA)

and found that US actually picked up on significant improvements in VL cross sectional area, whereas DEXA did not note the increased lean thigh mass (Scanlon et al 2014). Unsurprisingly, the US depth measures of the mid-VL correlated strongly and significantly with anthropometric (girth measures) assessment of the mid-thigh (MTC) (VL depth, total muscle depth, fat depth, r=0.44-0.67, p<0.01, Table 6.2). However, fat depth correlations with MTC alone suggests it is adipose tissue that drives the association (r^2= 0.45) and not the muscle mass, architecture, efficiency of contraction or force-production.

One major advantage of using US over anthropometric measures of the same site (e.g. mid-thigh circumference) is the ability to measure the muscle size and depth with greater accuracy without being as affected by possible oedema (swelling due to water retention). However, there are still limitations of using US in chronically and critically ill patient groups who are often vulnerable to oedema (as in the CKD population). US measurements can be confounded by oedema as it can distort the images and can cause problems in attempting to de-limit individual muscles within a muscle group (Gerovasili et al 2009). An example of this is the primary muscle group examined in this thesis; the vastus lateralis within the vastus group of the quadriceps (particularly determining the aponeurosis between the vastus lateralis [VL] and vastus intermedius [VI]). Despite this limitation, it is still a better choice for increased accuracy of measurement, as a skilled technician is able to determine early on whether the image brightness and tone can be adjusted to improve viewing or if some measures are not feasible in an individual (e.g. a researcher/clinician/ technician can still take a measure of total muscle depth, if unable to measure VL-only depth due to an indistinguishable aponeurosis).

8.2.1.1 Muscle quality

The advantage of a pennate-muscle is the increased potential for force production within the muscle. Comparative research examining body builders and sedentary individuals demonstrated that greater muscle hypertrophy was strongly linked to greater angle between the muscle aponeurosis and an individual muscle fibre (pennation angle; Kawakami et al 1993). The larger angle reflects the larger quantity of protein within both the muscle and systemically (assessed by the concentration of serum albumin), whether due to the CKD stage (later stages, less protein, smaller pennation angle; Chapter 4 and Chapter 6) or as a result of a training programme (increased anabolism and/or decreased catabolism, leading to increased protein stores, larger/steeper pennation angle and muscular hypertrophy; Chapter 7).

Muscle quality is assessed by a variety of methods; one is as muscle-force per unit of mass (force per physiological cross-sectional area [PCSA], Matschke et al 2010a). Muscle quality can also be assessed as echo intensity using ultrasound scanning, where an increase in the echo-intensity of a muscle represents changes caused by increased intramuscular connective and adipose tissues (improved muscle composition of connective to contractile tissue; Fukumoto et al 2012; Scanlon et al 2014). This thesis did not examine echo-intensity as a descriptor or marker for muscle quality but instead focused on other components that contribute to assessment of muscle force - namely fibre (fascicle length), pennation angle, muscle thickness and ACSA (not PCSA).

The specific tension of a muscle is determined as muscle force per PCSA. However, to calculate the PCSA of a muscle, volume, muscle fibre length, and fibre pennation angle must be determined (Kawakami et al 1994; Aagaard et al 2001) which in itself is time consuming and hard to measure precisely. Depending on the speed of

movement in the maximal strength tests, best measurement practise has been shown to vary; in knee extension exercise, muscle volume had the highest correlation at slower speeds but was not statistically better than ACSA and PCSA. At faster speeds PCSA x fascicle length and ACSA were better predictors than volume. However, muscle ACSA consistently came second at all speeds (Blazevich et al 2009), deeming it potentially the most useful measure across the board. Unfortunately, of the muscle measures taken using ultrasound in this thesis, ACSA was shown to have the greatest typical error (0.61 cm^2, Chapter 5). As previously mentioned, this is likely due to the greater potential for error in the configuration of individual images to form the full ACSA image, which is then measured. Due to the larger error within repeated measures, or between subjects, utilising another measure as a representative for ACSA would be a reasonable suggestion and the strong correlations (Chapter 6) observed between US-derived measures of muscle size showed potential (total muscle depth and VLACSA, r=0.48, n=17, p=0.04; total muscle depth and VL depth, r=0.85, n=20, p=0.00; pennation angle and mid-VL depth, r=0.58, n=8, p=0.08 [ns]; correlations between architecture [pennation angle] and mid-VL depth may have reached significance with a greater sample size).

When incorporating results from the intervention study (Chapter 7) where only VL ACSA and VL pennation angle showed interaction effects (greater effect size with greater training frequency or volume), the use of a single measure of either total muscle depth or VL muscle depth, would not have captured this highly significant difference. However, it is feasible that a single measure that did detect the differential effect of training frequency (VLACSA or pennation angle) alongside another simpler muscle (depth or thickness) measure would provide sufficient information to describe and interpret the results of an intervention (or observational) study effectively.

An alternative proposal that VLACSA and pennation angle could be used interchangeably, or as proxy measures/markers for each other was shown to be

invalid based on these results, as correlations between the two were far from the accepted level of significance (VLACSA and pennation angle, r=0.54, p=0.11), though once again this may be due to the small sample size (n=8). Previous studies into the relationship between muscle ACSA and architecture (pennation angle) have found instead that they are indeed significantly correlated, though were in very different populations (tricep brachii, body builders, r=0.83, p<0.001; weightlifters, r=0.68, p<0.001, Ikegawa et al 2008).

The US used in this thesis was a 2-D B-mode US, providing a two-dimensional image in a single plane at any one time. This can be used to measure muscle thickness (or depth) and to build an image (from several) to assess ACSA. However, to determine muscle quality it has been deemed useful to have a measure of muscle volume to calculate PCSA and using muscle force (strength) per PCSA to assess quality (efficiency). Previous literature has examined the validity of using a 2-D US to measure muscle volume (and compared it to volume measured by MRI). The authors (Miyatani et al 2004) found that muscle thickness is a good predictor of muscle volume when combined with limb length but found large variability of the contribution of muscle thickness to volume (i.e. they could not develop prediction equations based on thickness and limb or muscle length alone; Miyatani et al 2004). Based on the mathematical principles developed by Cavalieri (the method of indivisibles: e.g. the volume of a sphere or cone; Weisstein, 2014), others have calculated muscle volume with great accuracy (ICC>0.8, error 0.4 ± 6.9 %) from VL ACSA measures using two-dimensional US, with results validated against hydrostatic weighing (cadavers) (Infantolino et al 2007). However this is very time-consuming as it relies upon obtaining accurate ACSA outlines (perimeters) at multiple points along the muscle. An alternative - though very crude - version of this method would be to use one ACSA value and multiply by the muscle or limb length. Obvious inaccuracies ensue as neither the VL or quadriceps muscle is a standard cylinder,

and thus would either over- or under-estimate the true muscle volume, depending on the site of the measured ACSA.

Three-dimensional US is a viable option to reduce error in assessing the volume of non-standard shapes. It has been tested for validity in animal models against hydrostatic weighing (water displacement) to assess organ volume. As with 2-D US (and Cavalieri's method) there was a small error of 0.6% (Martins et al 2007).

Relevant and helpful though muscle volume is - particularly in establishing the degree of muscle quality - it is not necessary in repeated measures to track the wasting or hypertrophy of an individual or group. The limb length will remain unchanged, and the muscle length variability will be negligible across an intervention or observational study. Any atrophy or hypertrophy generally is most noticeable at the bulk of the muscle (e.g. the mid-point of the VL muscle) and thus for purposes of reporting change, using the ACSA is feasible, practical and reliable.

8.2.2 Comparison of early and late stage CKD

Initial findings show that there is a distinct difference between early stage CKD (CKD3) and those on dialysis (CKD5/ESRD/RRT). This was particularly evident in clinical measures, uraemic symptoms, and anthropometric (limb girth) measures as the lower levels of serum albumin - the most abundant protein in human blood plasma - reflects the comparatively reduced total body protein assumed through loss of muscle/other lean mass in the later stages of CKD (CKD5).

The expectation is that reduced strength and function comes with reduced muscle mass and activity level. However, whether the loss of strength and functional capability (increased fatigue, generalised weakness) associated with CKD is caused

by the loss of muscle mass, or conversely the loss of protein due to uraemia leads to decreased muscle - and therefore reduced activity level and consequent decline in strength and function - remain unclear. Nevertheless, the correlations between disease-stage, muscle (protein) mass, strength, function and frailty are evident throughout this thesis (Chapters 4 and 6) and previous literature (Castaneda et al 2001; John et al 2013; Johansen et al 2013). As mentioned previously, loss of muscle mass only partially explains the loss of muscle strength (loss of strength, dynapaenia; Manini & Clark 2012; Clark & Manini 2008) and previous research into a healthy but aged population demonstrated that the area of the quadriceps muscle only explains approximately 6-8% of variability between subjects in knee extension muscle strength (Delmonico et al 2009). Suggesting that muscle weakness is possibly more related to impairments in neural (central) activation and reductions in the intrinsic force generating capacity of skeletal muscle (Kostek & Delmonico 2011).

It is well known that muscular strength (Kamel 2003) and function (Bohannon et al 1984) also generally decrease with age, and epidemiological data shows the incidence and prevalence of CKD increases with age (2012 UK Renal Registry annual report, 2013), inferring that the loss of muscular strength and function will go hand-in-hand with increased risk of developing CKD. A number of studies have reported a deterioration of physical function in dialysis patients (Painter 2005; Johansen 2007; Johansen et al 2013) but only a few have examined physical function in pre-dialysis CKD patients (Hiraki et al 2013; John et al 2013). According to those reports, patients with pre-dialysis CKD are similar to dialysis patients in that they show lower knee extensor muscle strength and reduced exercise tolerability compared to healthy subjects (Heiwe et al 2001; Padilla et al 2008). The results from this thesis were not compared to a healthy population; however, a similar difference was seen between the two groups (CKD3 and CKD5) as was previously reported by Hiraki et al (2013) for these same stages which indicated even more specifically that this downward trajectory accelerates significantly after CKD stage 3 (CKD2-3 mild-

moderate reduction in GFR relatively stable functional ability), as CKD4-5 patients (severe reduction in GFR and renal failure) have significantly reduced physical strength and function compared to both the earlier stages and healthy (matched) controls (Hiraki et al 2013). These results were comparable to the measures within this thesis (Chapter 4), reporting similar clinical and strength measures in each group (Table 8.2). Although the subjects in the published data were stronger in both groups, the reduction was at a similar rate (e.g. KEPF).

Table 8.2 – Comparison of published results (Hiraki et al 2013) with current thesis (Chapter 4)

	CKD3 (Chapter 4)	CKD3 (Hiraki et al 2013)	CKD5 (Hiraki et al 2013)	CKD5 (Chapter 4)
GFR (m*L/min*)	45.7 ± 7.0	42.8 ± 9.8	10.1 ± 1.3	≤15
Hb (*g/dL*)	13.7 ± 1.8	12.8 ± 1.8	9.8 ± 1.1	11.5 ± 1.3
Serum Alb (*g/L*)*	41.8 ± 3.0	40.0 ± 3.0	38.0 ± 3.0	38.2 ± 4.3
Handgrip (*kg*)	27.4 ± 11.8	30.8 ± 10.3	22.4 ± 7.9	31.3 ± 10.0
KEPF (*Newtons*) *	303.7 ± 134.5	384.0 ± 8.3	282.0 ± 9.6	254.0 ± 72.0

**data converted from alternative units in Hiraki et al (2013) to allow direct comparison; Presented as mean ± standard deviation; GFR = glomerular filtration rate; Hb = haemoglobin; KEPF = knee extension peak force*

Further differences between CKD3 and CKD5 arise when examining the correlations between US-derived measures of muscle size and fat depths at the mid-VL site with muscular strength (knee extension peak force). The expectation was that correlations would be similar across the disease trajectory stages, but this was not the case. Table 8.3a highlights these different correlations and associations with knee extension peak force (muscular strength).

Table 8.3a – Comparison of US measures of muscle size and fat depth, correlated with strength (KEPF45) at early (CKD3) and late-stage (CKD5) CKD

Participant demographics	CKD3 (Chapter 6)		CKD5 (Chapter 5)	
N (M:F)	51 (28:23)		20 (18:2)	
Age (*years*)	59.9 ± 13.9		56.5 ± 16.7	
Height (*cm*)	165.2 ± 9.3		170.1 ± 7.4	
Body mass or weight (*kg*)	77.3 ± 14.2		78.0 ± 15.4	
BMI (kg/m^2)	28.1 ± 4.5		26.8 ± 3.8	
Total body fat (*%*)	32.5 ± 9.0		No data	
KEPF45 (*Newtons*)	303.7 ± 134.5	Correlation *(r)*	254.14 ± 108.00	Correlation (*r)*
VL ACSA (cm^2)	17.5 ± 3.6	0.35* (n=34)	17.8 ± 2.8	0.61** (n=19)
VL depth (*cm*)	2.2 ± 0.4	-0.12 (n=39)	1.9 ± 0.4	0.50 * (n=22)
Total muscle depth (*cm*)	3.9 ± 0.7	0.13 (n=39)	3.6 ± 0.7	0.49 * (n=22)
Fat depth (*cm*)	1.3 ± 1.0	-0.65**(n=39)	1.1 ± 1.0	0.23 (n=22)

Presented as mean ± standard deviation; BMI = body mass index; KEPF45 = knee extension peak force at 45 degrees; VL = vastus lateralis; ACSA = anatomical cross sectional area

Based on the demographics shown here (Table 8.3a) and in the earlier chapters, it is clear that CKD5 patients are statistically worse-off than CKD3 patients, as expected (lower peak force measures, alongside generally smaller muscle mass). However, the confusion of the correlations suggests other elements are in process here. Examining the participant demographics, it is notable that they are a relatively homogenous group (close in age and BMI). However, the gender split is not an even one (CKD3 55% male; CKD5 90% male) which will have contributed to the height, weight, BMI and body fat percentage difference and subsequently the varying correlations (gender difference in CKD3: height, body fat %, VLACSA, fat depth, KEPF45, $p<0.01$; and additionally body weight in CKD5, $p<0.01$, but not VLACSA).

By examining male-only data (Table 8.3b), we can see that the strength difference between the groups becomes greater as does the muscle size (though not to the same extent) which could theoretically change the consistency of the correlations.

Table 8.3b – Male-only demographics and US-derived body composition measures in early (CKD3) and late-stage (CKD5) CKD

Participant demographics (male only)	CKD3 (Chapters 4 and 6)	CKD5 (Chapters 4 and 5)
Age (*years*)	59.8 ± 15.2 (n=28)	58.0 ± 15.0 (n=90)
Height (*cm*)	170.9 ± 7.6 (n=28)	172.5 ± 7.5 (n=79)
Body mass or weight (*kg*)	80.2 ± 15.0 (n=28)	81.8 ± 16.0 (n=90)
BMI (kg/m^2)	27.3 ± 3.9 (n=28)	27.9 ± 5.0 (n=79)
Total body fat (*%*)	26.3 ± 5.7 (n=28)	24.0 ± 8.4 (n=9)
KEPF45 (*Newtons*)	382.6 ± 120.1 (n=20)	273.3 ± 68.9 (n=39)
VL ACSA (cm^2)	19.4 ± 3.1 (n=19)	18.1 ± 3.8 (n=18)
VL depth (*cm*)	2.2 ± 0.5 (n=28)	2.0 ± 0.3 (n=19)
Total muscle depth (*cm*)	4.0 ± 0.8 (n=28)	3.6 ± 0.7 (n=19)
Fat depth (*cm*)	0.6 ± 0.2 (n=28)	0.6 ± 0.2 (n=19)

Presented as mean ± standard deviation; BMI = body mass index; KEPF45 = knee extension peak force at 45 degrees; VL = vastus lateralis; ACSA = anatomical cross sectional area

This could be explored in greater detail with larger samples as a change in correlations between muscle size and strength (or function) and other factors along the disease trajectory could further inform the relative contributions of muscle wasting with neuromuscular strength and functional capacity. Similar investigations have been undertaken, examining the relationships between strength, function,

muscle fibre type, total body potassium (as an indicator for protein stores) and serum albumin with inflammatory markers (Castaneda et al 2001, 2004).

The research group (Castaneda et al 2001, 2004) found that the adaptations from a (12-week, 3x8@80%1RM) resistance training intervention (with low protein diet) in a NDD population, were correlated with a reduction in pro-inflammatory cytokines (IL-6 and the size of type I muscle fibres r=-0.58, p=0.02, and type II muscle fibres r=-0.68, p=0.05). The authors concluded that RT may therefore reverse the malnutrition-inflammation complex syndrome of CKD implicated in poor prognosis (Castaneda et al 2004). These clinical measures (markers of inflammation) may help develop prediction models for adaptation to a training intervention (based on circulating cytokines), or measure responsiveness to the exercise stimulus.

8.2.3 Anabolic (resistance exercise training) intervention

The 12-week resistance exercise training in early stage CKD patients had a positive effect for measures of muscle size and architecture, strength, function, and uraemic symptoms (HRQoL). This beneficial change was broadly similar in both groups (RT1 and RT3) except in measures of VL ACSA and VL pennation angle at the VL mid-point (summarized in Table 8.1).

This general improvement was anticipated, though the expectation would be that greater volume (frequency) of exercise would bring about a greater volume of adaptation even if not at the same rate (dose-response). However, it has been suggested that for individuals that are deconditioned - such as those with chronic illness, the frail or elderly - a training threshold may exist. That is, for initial training adaptations amongst the most deconditioned, when a threshold-stimulus is met,

further increases in volume load or frequency may not result in greater gains in strength (Benton et al 2011). The results of this intervention study (Chapter 7) reflect this proposition, as the significant group differences noted in body composition and structure did not occur in the initial stages, and it was only with more prolonged exposure (beyond eight-weeks of training) that they became apparent, and group responses began to diverge.

Whether this was the most effective intervention programme (3 sets of 8 repetitions at 80% of 1-RM) that could have been implemented is debatable. Literature has suggested that using an alternative "single set to failure", instead of the standard multiple-set protocol, may be a greater stimulus to promote adaptation in strength and muscular hypertrophy. The theory is that as the motor units used to perform the exercise are fatigued, the continued resistance causes higher threshold motor units to be employed (greater contribution from type 2b/fast twitch muscle fibres), which are capable of the greatest increases in strength and hypertrophy. Training to failure, when implemented, should be at a high enough intensity to stimulate an adaptation; suggested at 80% 1-RM (Stone et al 1996); the same intensity as instigated in the intervention study here (Chapter 7). However, training to failure should not be performed repeatedly for long periods due to the high potential for over-training or injury (reviewed by Willardson 2007), and it is not recommended for older adults, and those with pre-existing musculoskeletal or cardiovascular conditions (Stone et al 1996), and thus would exclude a large proportion of CKD patients (CVD is the number one cause of death due to complications as CKD progresses to ESRD; Go et al 2004).

8.2.3.1 Muscle size, architecture and force production

The inconsistency of muscle size adaptation and strength in response to the intervention (no group difference in maximal strength, but a dose-response [group

difference] in VLACSA and pennation angle) may appear initially to be counterintuitive as muscle force-generating properties are strongly influenced by the architectural arrangement of the fibres (Malas et al 2013). However, these results have previously been observed (reviewed by Kawakami 2005). It is now widely accepted that muscle hypertrophy accompanies an increase in pennation angle, reaching values as high as 55° (Kawakami et al 1993, Kawakami 2005) but an increase in pennation angle can lead to a muscle force deficit due to change in the efficiency of force transmission from the fibres to the tendon (Kawakami 2005). This has been disputed, with the expectation of increased muscle force and performance with increased pennation angle (in pennation angles below 45°; Malas et al 2013). The variation in the literature may be in part due to the methods used for the assessment of muscle strength. By measuring the change in peak isometric force using leg press and knee extension but only the change in pennation angle (and ACSA) of one of the multitude of muscles involved in the movement, one may suggest that many other important factors are not being assessed. The VL (measured in this intervention) is only one of four muscles of the quadriceps, which does not bring about movement and force in isolation of the others (Blazevich et al 2009).

A recent study of healthy, older (>60 years old) people showed no significant changes in pennation angle of the vastus lateralis muscle (3.3% increase, 6-week duration, Scanlon et al 2014). This is in contrast to the initial 6-weeks of the current intervention, where gains of approximately 10% (Figure 7.16b) were observed. This may be due to the slightly lower intensity of training dose experienced by the participants (~70-85% 1RM based on a subjective assessment of RPE of 5-6/10; Scanlon et al 2014) in contrast to this study. However, the population sample, though aged and therefore likely to have decreased muscle size and pennation angle (Doherty 2003; Cadore et al 2012), were not categorised as frail or deconditioned, nor were they uraemic; all factors potentially influencing the

baseline pennation angle. However, previous interventions have shown gains varying from 13-22% over an intervention period of 12-14 weeks (Reeves et al 2004; Suetta et al 2008) with suggestions of up to 35% improvements with eccentric training (Reeves et al 2009), closer to the results observed here (RT3 pennation angle ↑36% by week 12, Figures 7.6 and 7.16b).

As with the VL pennation angle, VL ACSA increased at different rates over the 12-weeks between the groups (RT3 ↑30.8% ↑5.64cm^2, RT1 ↑13.2% ↑2.52cm^2) culminating in a 3.12cm^2 difference between the two groups. These significant changes did not correspond with the changes in muscle thickness (total muscle depth and VL-only depth) in that these measures showed no group differences over the 12-weeks and the mean change was not to the same extent (VL only ↑9.7%, total muscle ↑8.6%). Initially this seems counter-intuitive but this has also been observed previously, where no significant change was observed in muscle thickness but dramatic (significant) change in VLACSA (VLACSA, ↑7.4%, $p<0.05$, VL depth, ↓7.3%, ns, Scanlon et al 2014).

Anatomical cross-sectional area has therefore been suggested as providing a more sensitive assessment of total hypertrophy as it has been reported to better relate to the hypertrophic and force-producing characteristics associated with muscle size (Bemben 2002). There is some variation in reporting, as often studies report total ACSA at the mid-VL point ("total quadriceps", or "knee extensor" area) and not just VL ACSA. Healthy individuals' quadriceps ACSA assessed by highly sensitive MRI showed initial growth and adaptation from 10-days into a high intensity resistance training programme (bilateral leg extension, 4 sets of 7 reps, "maximal", 3/week, Seynnes et al 2007). As previously mentioned, the deconditioning observed in the present study sample may have delayed the onset of muscular hypertrophy; however, the decision to measure VL ACSA alone (not total quadriceps ACSA) may

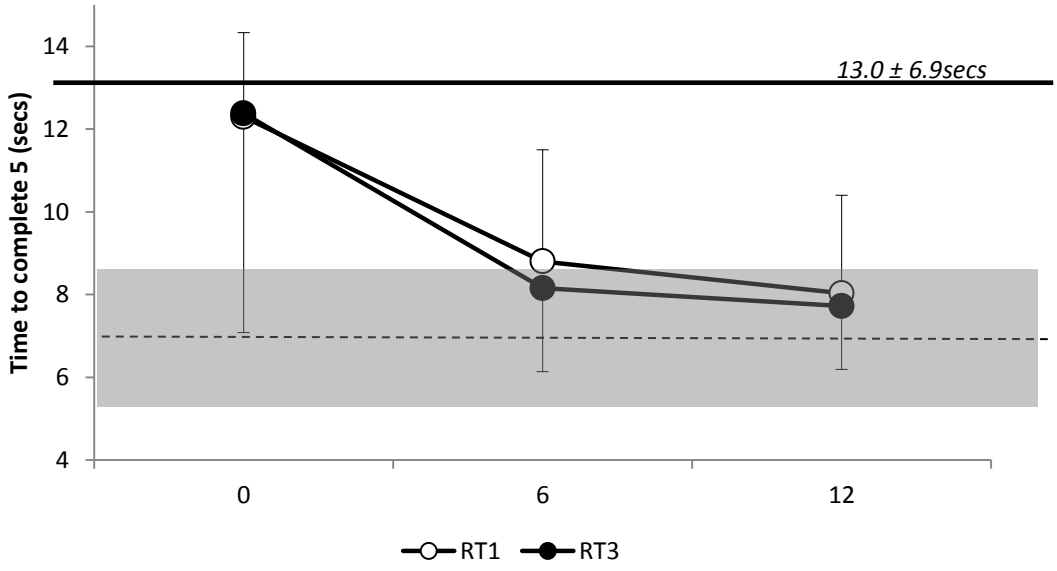
also have contributed to the delay as muscular hypertrophy will have taken effect in other trained muscles of the quadriceps, not just the VL.

8.2.3.2 Strength and Function, and the link with frailty

Muscular hypertrophy and changes to the architecture do not improve strength and functional performance alone. It is well-established that initial improvements in performance are instead due to neural adaptations as some studies have demonstrated increased strength in untrained limbs when the opposite was specifically trained (Enoka 1997; Zhou 2000). The intervention in the present study did not compare unilaterally trained limbs, but did examine upper body strength to control for systemic or pathophysiological adaptation. As reported in Chapter 7, handgrip strength did increase in both groups (RT1 ↑ 0.2kg, RT3 ↑ 0.6kg) over the 12-week intervention though neither measured change was significant ($p>0.05$) and were far below the MDC established in the literature (3.4kg, CKD HD, Segura-Orti & Martinez-Olmos 2011).

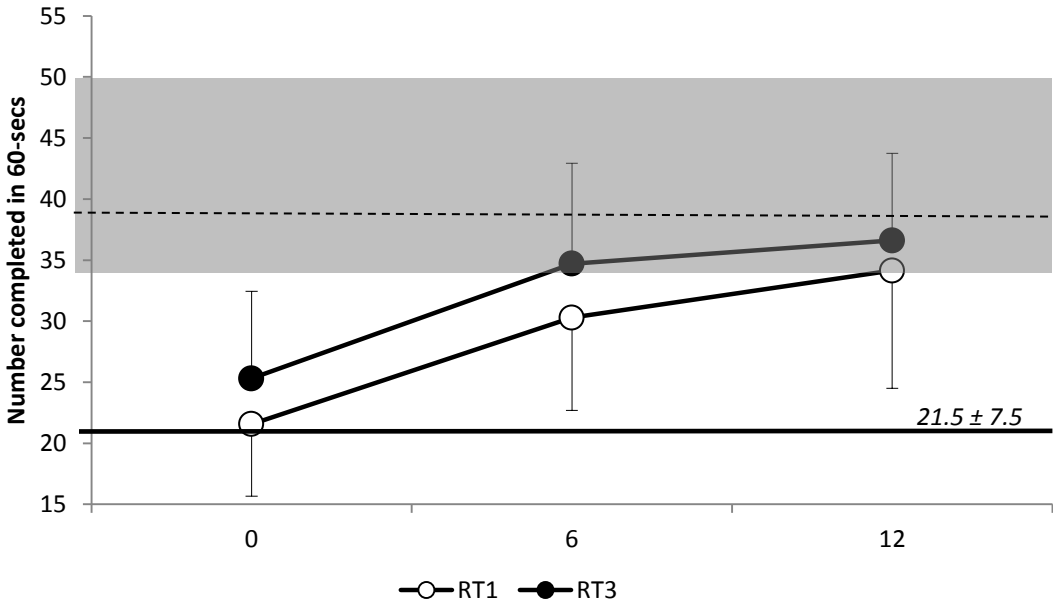
The pooled results from this intervention (Chapter 7) show a large adaptation effect in strength and function, especially when compared to patients later in the disease process. The two STS functional tests showed significant improvement over the 12-week intervention. It can be seen from Figures 8.1a-b that, on average, the resistance exercise intervention returned the functional capacity to within a normal "healthy" range by the mid-point (week six). The sample cohort for the intervention assessed in this thesis (CKD3) had a mean age of 56.9 ± 13.0 years.

Figure 8.1a – Change in STS5 (time) over the 12-week resistance training intervention



STS5: Dashed line shows average values in a healthy population of the same age range (50-59yrs) and shaded area shows the normal range (mean ± SD) within the healthy population (age 50-59 years, n=15, 7.1 ± 1.5 secs; average community dwelling adults, all ages 18-89yrs, mean 51 ± 20.8 years = 7.6 ± 2.7 secs; Bohannon 2007*). The thick black line represents the CKD5 average (13.0 ± 6.9secs,* Chapter 4*).*

Figure 8.1b – Change in STS60 (count) over the 12-week resistance training intervention



STS60: Dashed line shows the reference values from the 50th percentile for the 55-59 year age group, and shaded area the 25-75th percentile (25th percentile: 30 [female], 33 [male], 50th percentile: 36 [female], 41[male], 75th percentile: 43[female], 48[male]; Strassman et al 2013*). The thick black line represents the CKD5 average (21.5 ± 7.5,* Chapter 4*).*

The improvements in function - comfortably bringing the participants into the healthy (average) range - are an indication of increased independence and reduced frailty as these two measures (physical function and exhaustion) are commonly used in diagnosing frailty in the elderly or chronically ill populations. This is important as those deemed frail (low physical function, self-reported exhaustion, weak grip strength, slow gait speed and unintentional weight loss; Fried et al 2001)

are often transferred on to dialysis earlier in the disease process where dependence increases alongside a reduced HRQoL. Frailty has also been linked with increased risk of falls and increased hospitalization (Johansen et al 2013).

The STS5 outcome measure is usually cut-off (test is stopped) between 12 and 15-seconds (>65 years old, Buatois et al 2010; community dwelling elderly, Mong et al 2010; >60 years old community dwelling, Bohannon 2006), as over this duration the participant should be assessed for an increased risk of falls, with estimated values (mean time) for normal performance in community dwelling older adults falling around the 12-second mark (60-69 years, 11.4 sec; 70-79 years, 12.6 sec; 80-89 years, 12.7 sec; Bohannon 2006). Figure 8.1 clearly demonstrates the sample population from this intervention reducing the average scores from that cut-off point where there is increased risk of falls to a level much more appropriate for the age group. Although it would also appear that the improved function did not reach the upper-half of the healthy-average from this 12-week resistance training intervention.

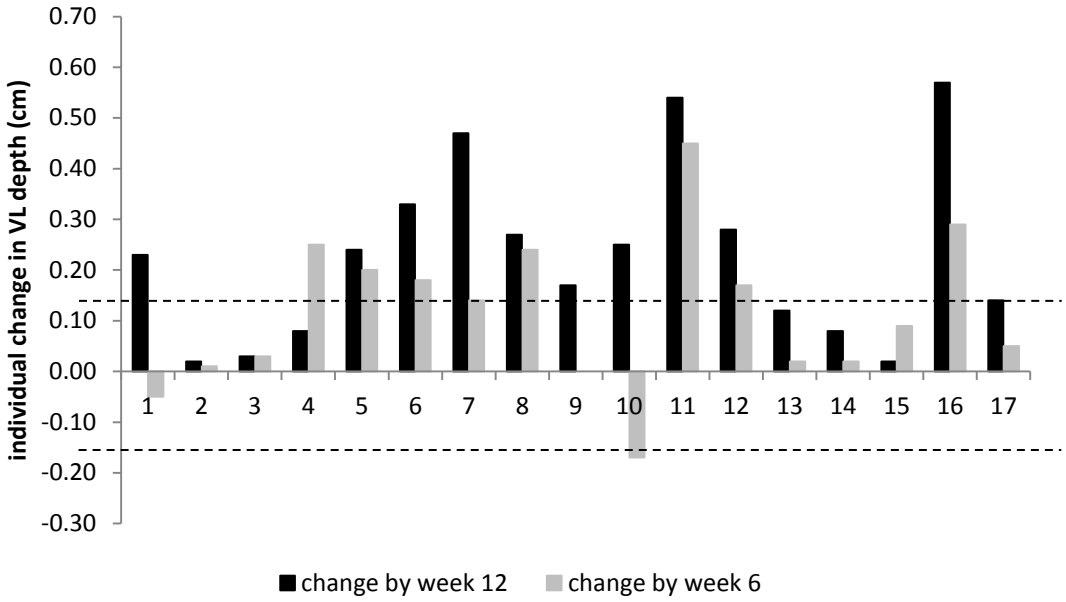
8.2.4 Responders and non-responders to the intervention

It has been previously demonstrated that for 20-25% of participants undertaking an exercise programme there is little to no favourable response (Davidsen et al 2011; Timmons et al 2010; Timmons & Phillips 2014) whilst a small percentage (5-10%) suffer adverse events (Bouchard et al 2012). Fortunately in this intervention there were no reported adverse events but approximately one-third of participants did not meet or exceed the MDC in VL depth, indicating a lack of response to the exercise intervention (Figure 8.2).

Similar non-responsiveness to an exercise intervention has been reported in ESRD patients where average results demonstrated a significant increase, but the wide

standard deviations indicated a large heterogeneity within the sample (6-months, aerobic training, Koufaki et al 2002). With individual assessment, the authors identified non-responders (61% responded by 3-months, 89% by six-months in VO_2peak) as those not reaching the standard error of the mean (similar to MDC [MDC = (1.96)(√2)(SEM)]), and gave potential reasons as non-compliance (unable to complete the exercise prescription), the limiting effect of co-morbidities, or a genetic pre-disposition to non-adaptation to an exercise stimulus. The genetic influence on adaptation/ responsiveness has been postulated previously (review update: Perusse et al 2013), though this has largely examined aerobic/endurance training responses (VO_2peak/VO_2max, submaximal performance, cholesterol, blood pressure, and heart rate; reviewed by Bouchard & Rankinen 2001) and requires further investigation, especially within specific populations (such as CKD), though it is likely to be applicable to all populations due to the nature of genetics.

Figure 8.2 – Individual change data from baseline, dashed lines represent the MDC using 2-D B-mode ultrasound in the CKD population (VL depth MDC: ± 0.14cm, chapter 5). Participants 1-10 were in group RT3, and 11-17 in RT1



The non-responders - determined by change in VL depth - appear to be distributed across the two groups, with a greater proportion in RT1 (3/10 not reaching the MDC by week 12 in RT3, 4/7 in RT1).

From the graphed individual change data for strength (Figure 8.3), function (Figure 8.4), and uraemic symptoms (Figure 8.5), it can again be seen that the non-responders are equally distributed across the two groups (participants 1-10 in RT3, and 11-17 in RT1) for outcome measures that showed no group*time interaction.

Figure 8.3 – Individual change data for strength (KEPF45 and LPPF45) (MDC: KEPF 46-79N; Bohannon 2012)

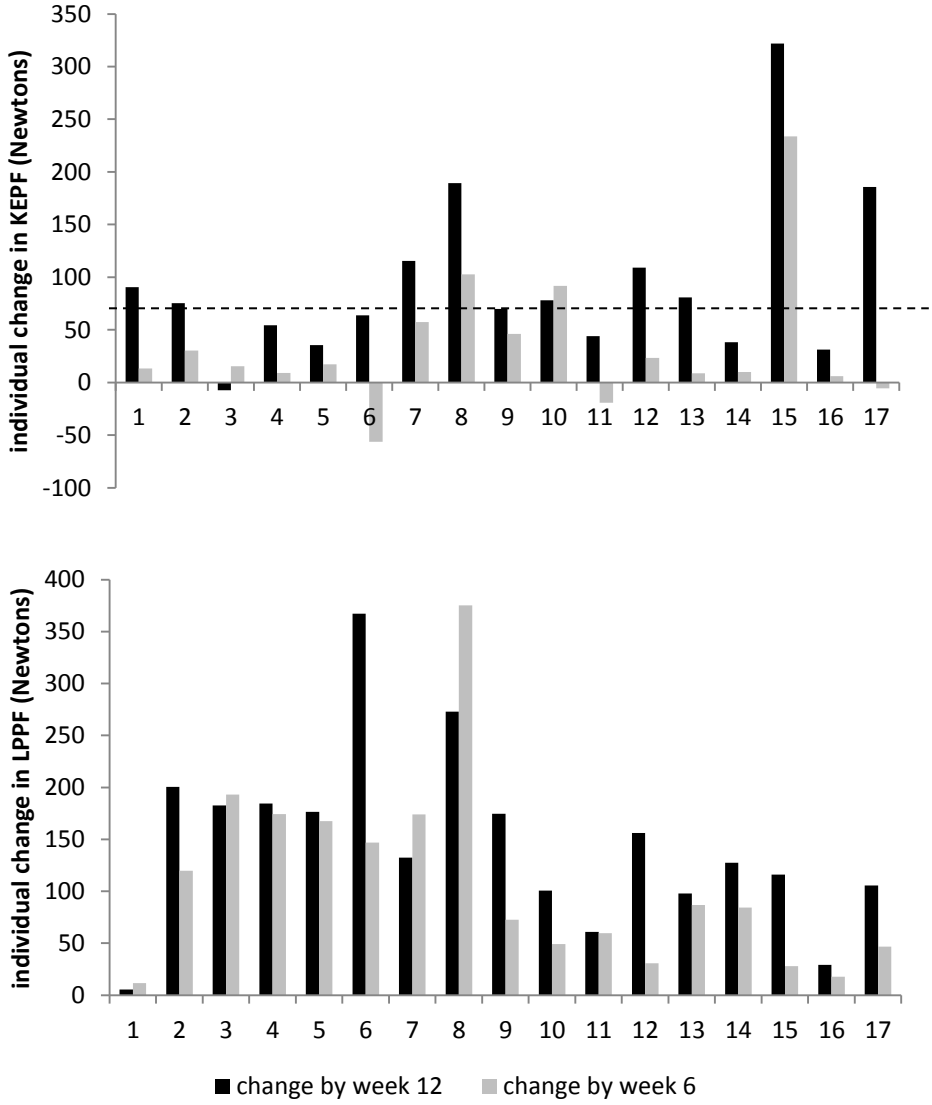


Figure 8.4 – Individual change data for functional tests – STS60, STS5, NSRI walk test. Dashed lines represent the minimal detectable change (MDC). Change greater than this line represents a response to the intervention (MDCs: STS60: 4-repetitions, Segura-Orti & Martinez-Olmos 2011; STS5: 1.7 - 3.12 seconds, Jones et al 2013, Goldberg et al 2012, Puthoff & Saskowski 2013).

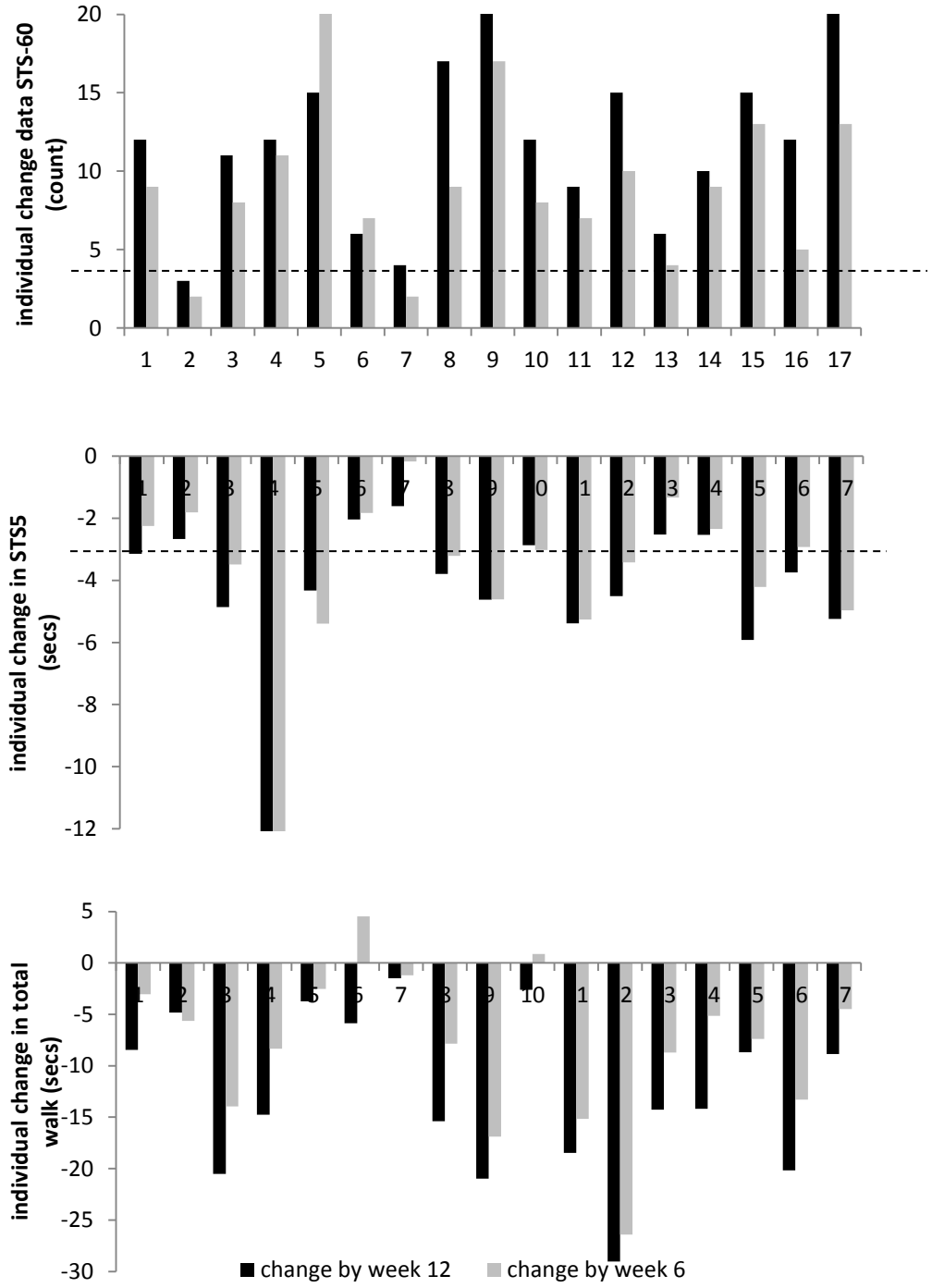


Figure 8.5 – Individual change data for uraemic symptoms (LUSS) from baseline to week 12

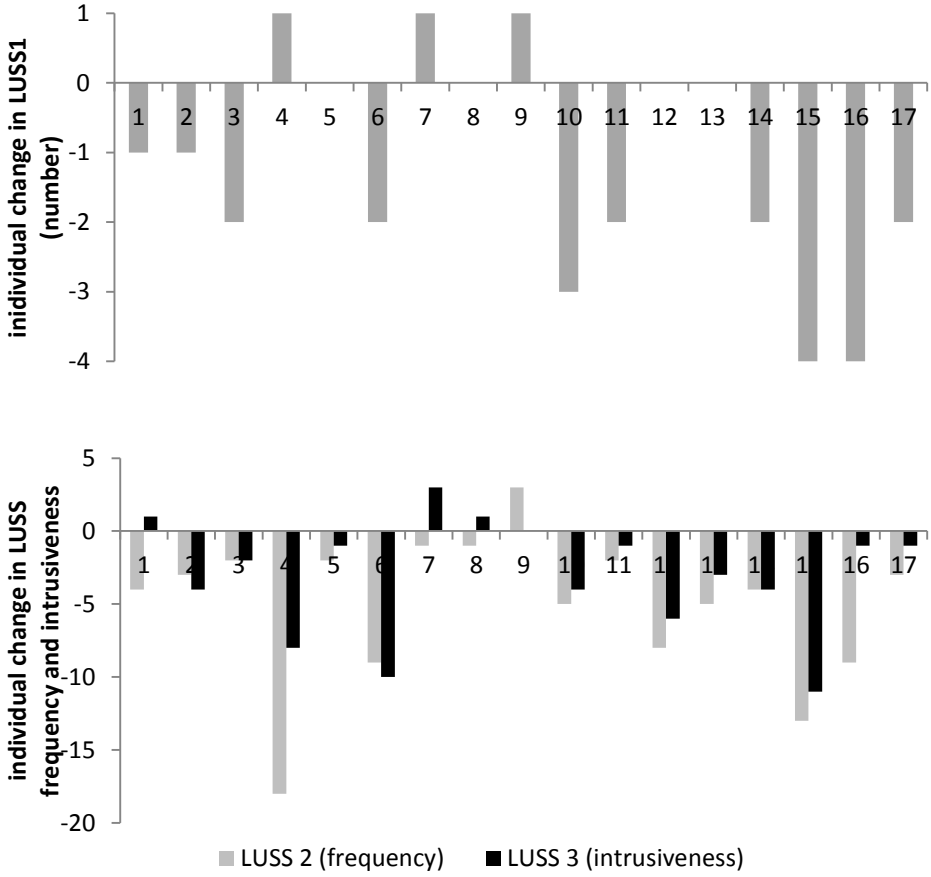


Table 8.4 – Overview of responders and non-responders (by participant number) based on outcome measures with previously calculated or published MDCs

By week 12	VL depth	KE PF 45	STS 60	STS 5	LUSS 1	LUSS 2 and 3
Apparent non-responders	2, 3, 4, 13, 14, 15	3, 4, 5, 6, 11, 14, 16	2	1, 2, 6, 7, 10, 13, 14	4, 5, 7, 8, 9, 12, 13	1, 7, 8, 9
Largest response	7, 11, 16	8, 15, 17	8, 9, 17	4	10, 15, 16	4, 6, 15

Table 8.4 summarizes the responders and non-responders to the full 12-week intervention. It is apparent that some participants struggled to make gains in some assessments but not in others. For example, some of the best responders to the intervention with regards to muscle size were participants #7, 11, and 16 though each also appeared as non-responders in strength (KEPF: #11, 16), function (STS5: #7) and uraemic symptoms (LUSS: #7) and vice versa (non-responder in VL depth, but greatest response in KEPF, and LUSS: #15). This suggests that adaptations are made by each participant in a response to the intervention; however, not all participants adapt in the same manner.

The suggestion that all participants adapt in some way to the intervention is highlighted further when examining group differences for outcome measures with a group*time effect (pennation angle and VLACSA).

Figures 8.6 and 8.7 clearly demonstrate that all participants adapted to some extent to the intervention (all show a positive change by week 12), and demonstrate an apparent dose-response (RT3>RT1), as the individual change of the pennation angle and VL ACSA show the increased rate of change in those training three-times per week, compared to once per week.

Figure 8.6 – Individual change data for pennation angle of the VL muscle. Participants 1-10 were in group RT3, 11-17 in RT1.

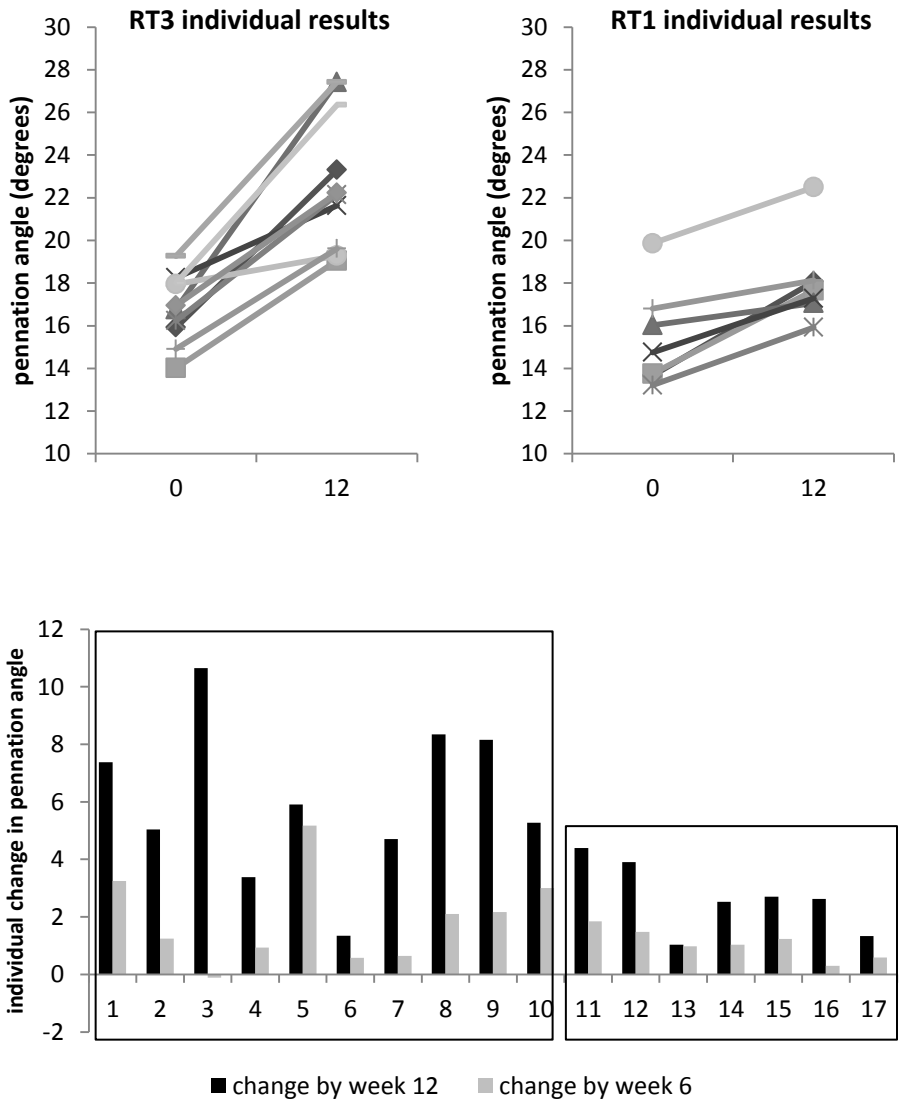
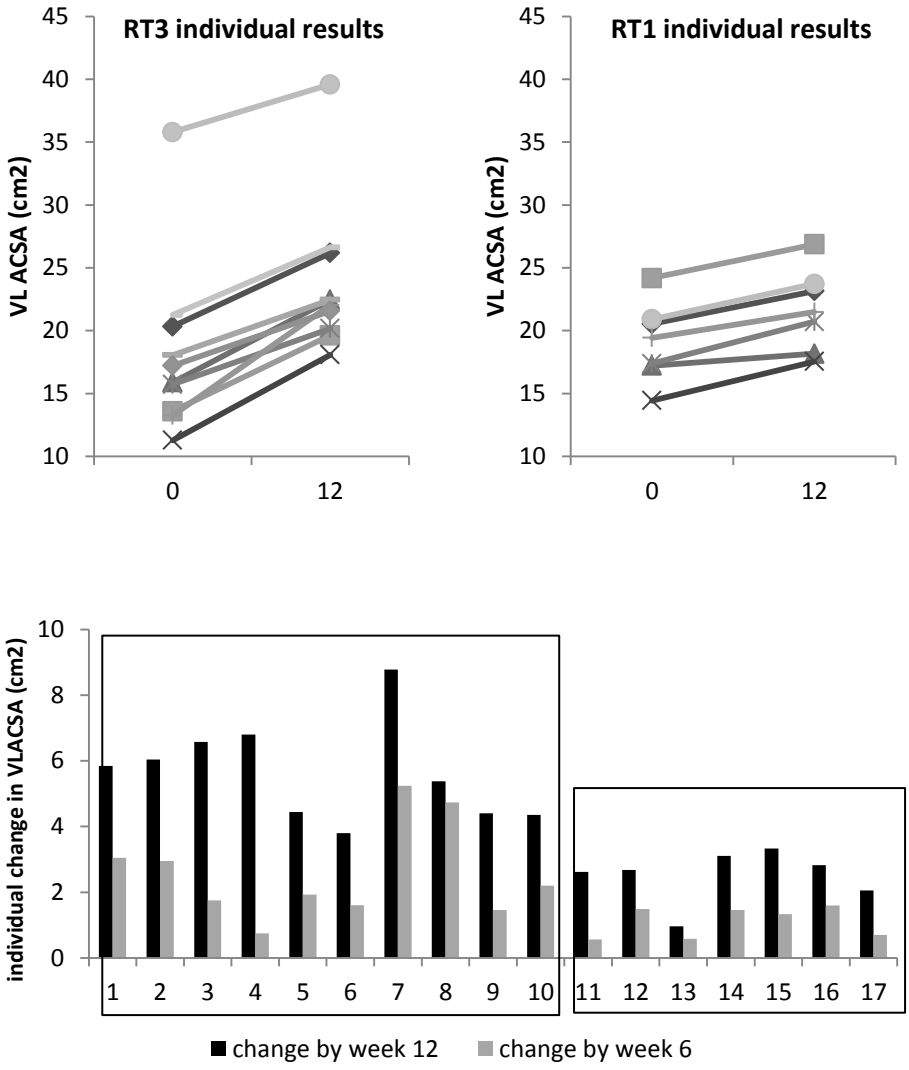


Figure 8.7 – Individual change data for ACSA of the VL muscle. Participants 1-10 were in group RT3, 11-17 in RT1.



The correlations calculated (Chapter 6) indicate that the change observed in both VLACSA and pennation angle at the mid-VL site is linked with change in strength (KEPF45 in particular; VLACSA and pennation angle both r=0.35, p<0.05, Table 6.2), so other factors account for the majority (r^2= 0.12) of the varying response rates (no

group*time interaction for strength measures) and no simple relationship between ACSA or pennation angle, and strength exist.

For more exact prediction equations, or stronger relationships with muscle force production, it has been suggested that the physiological cross-sectional area (PCSA) is used. To calculate the PCSA, data is required regarding fibre length, pennation angle, and muscle volume (Aagaard et al 2001). Maximal contractile force relative to PCSA has been reported as remaining consistent across a variety of muscles in various animal models (Close 1972); though more recently a suggestion of greater variation in human skeletal muscle has been made (Aagaard et al 2001).

When examining individual data for VL ACSA and pennation angle, where there was a group*time interaction (differential response to training volume; RT1 or RT3) it is clear that all participants in this sample adapted in response to training. How this adaptation manifested varied between individuals.

Despite initial individual analyses showing a split of responders and non-responders, certain measures showed improvements for all participants (ACSA and pennation angle), alongside varying responsiveness in other outcome measures. Firstly, these results need to be replicated as the sample was small, and a larger (and broader) cohort may not demonstrate the favourable adaptations seen here. Assuming these results are accurate, then all CKD3 patients may have the ability to adapt to a resistance exercise stimulus in some capacity, though a more tailored approach (personalised medicine) may be necessary to elicit the required and/or desired response. Knowledge of the genetic phenotype of an individual may contribute to improved interventions as this is likely to be the most influential factor.

8.2.5 Summary

The common pathway of protein-energy wasting and frailty has clearly been described (Delgado et al 2013), with the need for early intervention paramount to delay further deterioration.

Some studies that have brought about (or observed) improved protein synthesis, increased muscle size (measured by anatomical or physiological cross-sectional area, muscle depth/thickness, muscle volume) or improved architectural structure (pennation angle) have not necessarily demonstrated equivalent improvements in muscular strength or functional performance measures, and vice versa (peak force, sit-to-stand tests, walk tests; MacDonald et al 2005; Song & Sohng 2012; Tables 2.7a-b), though these variations were predominantly in dialysis (CKD5/ESRD) patient studies.

Decreased testosterone levels in CKD have been shown even in the early stages of the disease progression, which further contributes to the pro-catabolic environment that leads to muscle wasting and loss of muscular strength (CKD2-4; Cigarrán et al 2013). Increasing lean mass (through promotion of anabolism and hindering catabolism) via (non-medical anabolic) exercise interventions is the preferred method due to the other beneficial side-effects associated with exercise. However, prescribing a generic resistance programme may not be optimal, depending on the primary outcome objective.

8.3 Limitations of this thesis

The results of the intervention study are robust due to the effect size and significance of the adaptation to the intervention. However, results from the intervention study should be interpreted with some caution due to the small sample size recruited from a heterogeneous population (varying age, medical history and physical activity background), though this bias was reduced through the randomisation applied after baseline measures were taken.

With a larger sample size for the main intervention study it may have been possible to stratify the results into responders and non-responders to the intervention. This theory has been explored in previous exercise studies (in general population samples, Buford et al 2013; Stroke, Bowden et al 2013; COPD, Troosters et al 2001; CKD, Koufaki et al 2002). This would enable future interventions of this nature to be tailored to the individual based on the expectation of effective adaptation response; for example, if the non-responders had been limited by co-morbidities such as diabetes, other medical history, baseline outcome measures, clinical results or other factors.

A larger sample size would have also allowed inclusion of other intervention groups, including a standard control or usual care group. The lack of inactive control group means the results cannot be compared to the ongoing disease progression seen with usual care. It is possible that the additional (control) group may have affected the significance of the results either way and the ideal study design would have had four groups; RT1 and RT3, a standard control or usual care group, and finally a group with no structured or supervised intervention but advice to include resistance training into their lifestyle (to examine the effect of supervision and structure). This was not feasible in this study due to constraints of time and recruitment (participant availability). Additionally, whereas it was previously believed that for

CKD patients any intervention which induces movement or some form of physical activity (placebo, sham, or advice only) was sufficient to bring about a beneficial result, recent literature showed this theory (in layman's terms: anything is better than nothing) to be incorrect (Wang et al 2009). If this is the case, then excluding a group from the anabolic intervention by randomization to a control or usual care group could be deemed unethical (withholding a known beneficial form of treatment).

A further limitation of this thesis is that the comparison and correlation studies (Chapters 4 and 6) were only cross-sectional by design and did not follow the patient groups longitudinally to accurately describe and quantify the decline in mass, strength, function, and health-related quality of life. The inference that CKD5 fare worse than CKD3 across the variety of outcome measures is instead based on average measures in two distinct groups and cannot be reported with the same weight as individual change data denoting the natural history of decline across the established disease trajectory. This was again due to time-constraints and used a convenience sample at the two stages as only a small percentage of CKD3 patients would deteriorate/progress to CKD5/ESRD within a given time period (4% risk of progression to ESRD in 5.5-year follow-up; Drey et al 2003).

The validation and reliability of 2-D B-mode ultrasound was tested (Chapter 5) in CKD peritoneal dialysis patients (CKD5 CAPD), showing excellent results. However, the protocol, MDC, and typical error were then applied to early stage (NDD) patients. Both groups (PD and NDD) were CKD patients - of similar demographics - but this may have compromised the external validity of the measurement as it has been reported that ultrasound measures in different stages of wasting (sarcopaenia, Strasser et al 2013) have varying echogenicity or image quality (healthy muscle tissue is normally echo-lucent or dark, Mayans et al 2012). Fortunately, these studies have found that image quality and reliability is actually

enhanced in younger or healthier muscle tissue (Pillen & van Alfen 2011; English et al 2012), suggesting non-dialysis dependent (NDD) stages will give clearer images compared to those in dialysis dependent patients.

Finally, the Leicester Uraemic Symptom Score (LUSS) - used here as a proxy indicator for some aspects of HRQoL - is an assessment of eleven commonly reported symptoms of uraemia, of which approximately half are associated with weakness and muscle wasting. It was therefore not entirely unexpected that the reported symptom number, frequency and intrusiveness would reduce with the RT intervention as functionality and strength improved. Utilising another HRQoL test may have been more appropriate to gauge the more general changes or adaptations that may have occurred as a result of the intervention (or at different CKD stages). The Kidney Disease QoL (KDQOL) and the Short-Form 36 Health Survey (SF-36) have both previously been used in this population and found to be valid, with the SF-36 also being implemented in other chronic and critical illnesses. However, the LUSS design allows frequency of symptoms and intrusiveness to be assessed separately to prioritise treatment; a symptom may occur frequently but is not deemed intrusive to the individual patient. If the LUSS design was extended to include other common symptoms of uraemia (e.g. pruritus, anaemia, tachypnea/rapid breathing, dyspnea/shortness of breath, urination problems; Table 2.2) it could be of greater value in the assessment of HRQoL from an intervention.

Table 8.5 – Overview of the limitations of the thesis

Limitations
• Small sample size in the intervention study • Lack of standard control group for the intervention study • Cross-sectional study design for assessing differences between CKD stages • External validity of US to the CKD3 intervention sample • LUSS focus on only eleven symptoms

8.4 Implications for research, practice, and policy makers arising from this thesis

8.4.1 Policy-makers

Current guidelines for Chronic Kidney Disease include the advice that "CKD patients should be encouraged to take exercise" (NICE CG 73, 2008; Holt & Goldmith, The Renal Association 2011); however, there is no formal route or prescription/ explanation of exercise type, duration or intensity. This thesis provides evidence that a structured PRT programme brings about benefits to a number of the essential criteria that contribute to improved health-related quality of life (greater independence through improved strength, function and reduced uraemic symptoms).

Formal rehabilitation programmes exist for other chronic illnesses in the UK, implemented by the NHS or associated foundations/agencies (cardiac: British Association of Cardiac Prevention and Rehabilitation; pulmonary: British Lung Society) and advice exists to exercise during dialysis, but not in NDD patients. A recent systematic review and meta-analysis of PRT in all CKD stages also concluded that policy-makers and clinicians should look to prescribe PRT to induce muscular hypertrophy and improve strength and health-related QoL (Cheema et al 2014). This thesis provides a strong foundation for the initiation (or piloting) of a

programme similar to the exercise groups recommended for cardiopulmonary rehabilitation; with sessions held on a weekly basis.

8.4.2 Clinicians and Researchers

Other chronic illnesses have utilised 2-D B-mode ultrasound where muscle atrophy is a complication and limitation of the disease. This thesis has demonstrated that 2-D B-mode ultrasound is clearly accurate and sensitive enough to detect individual patient and group change over time in the CKD population, whether it is used to track the muscle size or architecture to monitor the effect of the disease progression, or in response to an intervention (anabolic: exercise, nutrition, hormonal; RRT: dialysis or transplant). Accurate measurement of body mass and composition is vital, and currently-used anthropometric, body mass and subjective global assessments do not have the level of sensitivity required.

The body-site used in this thesis (mid-VL) was selected for measurement (and training) due to the contribution of the quadriceps to many functional activities required for independence in daily life. The advantage being this is also a pennate muscle and the exercise intervention could affect the muscle architecture. Other pennate-muscles could be used to assess change (pennation angle; architecture) from training, disuse, or disease-related atrophy, though these other muscles/sites would need separate validation.

Table 8.6 – Overview of implications for research, practice, and policy-makers

Implications
• Policy-makers: look to implement a standard progressive resistance training (PRT) *prehabilitation* programme for early-stage CKD patients. • Researchers and Clinicians: using ultrasound is a practical and accurate way to measure and track muscle size and architecture at localised areas of the body.

8.5 Suggestions for future research studies arising from this thesis

A number of research studies can be suggested based on this thesis in participant/population, intervention, control/comparison, and outcome measures.

8.5.1 Participants/population and comparisons

The two main population comparisons would be firstly to include healthy or asymptomatic (disease-free) groups. This is important to confirm that CKD3 patients are already frailer than asymptomatic individuals as shown in the earlier literature (Wilhelm-Leen et al 2009) and to compare the adaptation rate in response to the training interventions performed here (RT1 and RT3). This would allow researchers to comment on the rate of change of the non-CKD compared to CKD individuals, to determine if there is a limitation enforced by the inflammation and uraemia experienced by these early-stage CKD patients.

The second population comparison to be introduced would be CKD4 patients. Once again the aim of the study would be to examine the adaptation rate, and extent of the adaptation possible, in comparison to both CKD3 and non-CKD participants. It has been strongly suggested that weakness and frailty in CKD becomes particularly pronounced in the transition from CKD3 to CKD4 (Hiraki et al 2013). Would this reduced strength, function and health-related quality of life remain below those of CKD3 and asymptomatic participants with the implementation of the RT programme? Or do these patients have the same potential for adaptation as these other two groups, considering that the previously implemented RT programmes in late-stage CKD (CKD5/ESRD/dialysis-dependent) patients have reported mixed results (improvements, no change, or reduction in muscle size and/or strength; Segura-Orti et al 2009; Headley et al 2002; Cheema et al 2011)?

8.5.2 Intervention

Follow-up of the current intervention sample would be interesting and important to determine the maintenance potential of the outcome measures (improved muscle, strength, function, health-related quality of life) and simultaneously examine the participants who continue with the intervention (without instruction or supervision) of their own accord (compare and contrast characteristics of those who do and do not continue, maintain, or respond).

Based on the results from this thesis, depending on the primary aim of the study would determine the intervention training frequency; if the primary aim is to (1) bring about improvements in strength, function and HRQoL, or to (2) bring about change in muscle size and architecture, will determine the intervention programme design -

(1) The results of the intervention in this thesis (Chapter 7) implied a greater adaptation rate per exercise training session in group RT1 compared to RT3, as similar changes from baseline were observed in VL ACSA after 18 sessions in RT3 and just 12 sessions in RT1, and pennation angle (RT3 18 sessions, RT1 8 sessions). From this it would be informative to extend the once per week training sessions (RT1) for a total number of sessions equivalent to those completed in 12-weeks in RT3 (36 sessions = 12-weeks RT3 = 36-weeks RT1), to observe whether this increased "efficiency" translates to a greater overall improvement over the complete 36 sessions. Advancing and extending this RT intervention once per week would also provide guidance to policy-makers initiating a programme of exercise for CKD patients.

(2) To bring about maximal change in muscle ACSA and pennation angle, with minimal participant time, intrusiveness, or commitment; implementing a training programme once per week for the initial six or eight-weeks, followed by increased frequency (to thrice per week) could bring about

equivalent growth as the current RT3 group (thrice per week from the beginning). This hypothesis is founded upon the similar improvements observed in the two intervention groups up to week eight, at which point muscle measures began to diverge. Additionally, by increasing the dose by this point (between 6-8 weeks) may stimulate greater improvement in strength, function, and uraemic symptoms in the second six-weeks instead of the relative plateau observed in both groups from the mid-point as they became accustomed to the stimulus frequency, even with the progressive nature of the training intensity (80%1RM); adaptation/recovery is accelerated allowing greater intensity within an individual session, even with the increased frequency (reduced recovery time).

8.5.3 Outcome measures

Objectively measuring physical activity outside of the intervention would allow researchers to eliminate the effect of outside influence. In the current study, the patient-reported physical activity recall (PAR) attempted to assess these differences between groups. However, due to the subjective nature of the test, precision may not be high enough for use as a co-variate (individual opinion of what is high/medium/low intensity, despite instruction and definitions provided). Introducing accelerometers would allow greater accuracy of activity levels outside of the intervention.

To minimise the time-taken and potential for error in the reconstruction of the ACSA image prior to measurement, introducing a proxy (or prediction equation based on simpler and consistently accurate US-derived measures) would be beneficial. This would have to be grounded on outcomes with high correlation between ACSA and the suggested proxy measures. Based on the correlations of US muscle measures taken in Chapter 6 and results of the intervention (Chapter 7), VL or total muscle depth (thickness) would not be able to provide sufficient

information alone (no difference was observed between groups whereas ACSA showed a significant difference). However, combining the thickness (depth) measure with pennation angle (which showed a group effect as well as time effect) may be sufficient. This would require a significantly larger sample than those used in this thesis but could be developed in healthy populations (for recruitment convenience) and adapted for the chronically ill populations if necessary.

Finally, as previously mentioned in the thesis limitations section, the LUSS could be further developed to provide more information on a broader array of symptoms that are associated with the inflammation and uraemia manifested in CKD patients, at any stage of the disease process.

Table 8.7 – Overview of suggested further research

Further research
Participants and comparisons: • Healthy comparison/control group • Implement intervention in CKD4
Intervention: • Follow-up current sample to examine maintenance levels • Extend the RT1 intervention to compare adaptations at the same total session number as RT3 • Examine starting the intervention at RT1 then increasing frequency to RT3 from 6-8 weeks
Outcome measures: • Objectively measure physical activity levels outside of the intervention (possibly use accelerometers) • Find a proxy measure and/or develop equations using simpler muscle measures than reconstructing VL ACSA from separate images • Develop the LUSS to include other common symptoms on CKD beyond the current focus

CHAPTER 9 - Conclusions

9.1 Main findings

There were two main findings arising from this thesis –

1. Assessing regional body composition using two-dimensional brightness-mode ultrasound (2-D B-mode US) as a measurement tool is valid and reliable in the CKD population.

It is also very useful; differentiating between tissues such as muscle and fat as well as allowing clinicians and researchers alike to view structural or architectural adaptation that may occur as the disease progresses or in response to an intervention. The main advantages of using ultrasound over other measurement tools which are also capable of doing this (such as MRI, CT, DEXA) are the portability (near-bedside method), reduced financial cost, and minimal intrusion to the patient/participant.

2. Resistance (exercise) training in early-stage CKD patients either once or three-times per week for 12-weeks brings about an anabolic response; significantly increasing muscle mass, strength, function and improving the muscle architecture in the trained muscles, alongside a reduction in the uraemic symptoms experienced by the patients/participants.

Positive results such as these have been observed in the CKD population, though the focus has previously been on dialysis-dependent patients (NDD: Castaneda et al 2001, 2004; ESRD: Cheema et al 2011; Segura-Orti et al 2009; MacDonald et al 2005). These previous studies have also largely compared a control (no intervention), endurance intervention, or placebo/sham training group to the resistance training intervention. Though this is methodologically advantageous (RCTs being the gold standard approach), these studies have generally implemented an intensive RT intervention (same as the high volume group here; 12-weeks,

80%1RM, three-times per week). The use of two intervention groups in this study has highlighted that the high volume/frequency intervention is no more beneficial to the patient/ participant than the low volume/frequency, as training either once or thrice per week brought about the same increases in strength, function and health-related quality of life (reduced uraemic symptom frequency and intrusiveness).

9.2 Clinical, practice, and research implications

The intervention results suggest implementing a resistance training (RT) form of "prehabilitation" in early stage (CKD3) patients just once per week is sufficient to bring about statistically and clinically important changes in strength and function that benefit the patient through reduced frequency and/or intrusiveness of uraemic symptoms (improved health-related quality of life), with minimal time-commitment.

Further research should examine if there is additional benefit to the significantly greater increases in VLACSA and pennation angle observed in RT3 with regards to long-term maintenance of functional improvements, and whether an RT1 or RT3 programme delays the progression of CKD, reduces/delays the need for RRT, and beneficially affects patient mortality.

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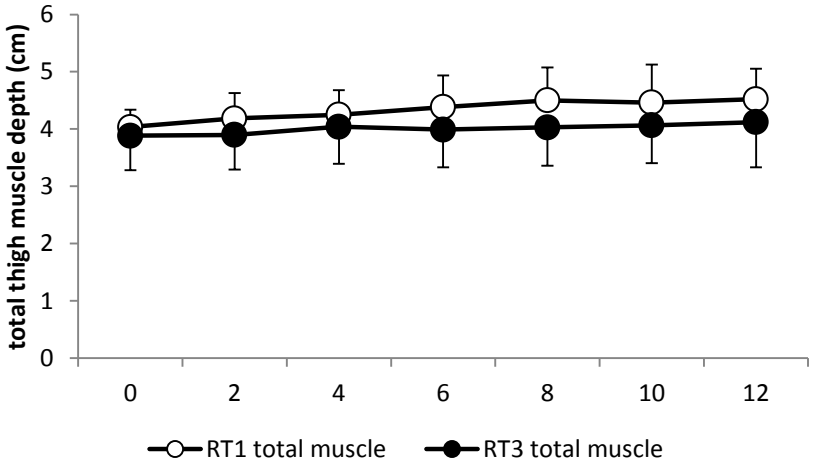
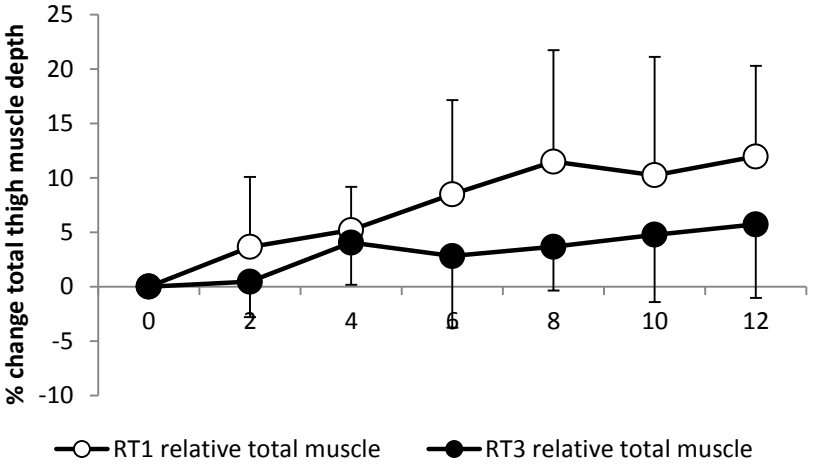
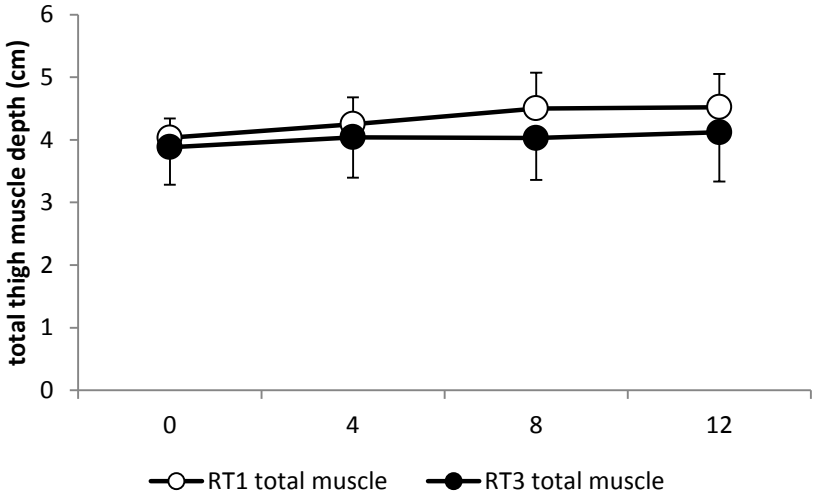
APPENDICES

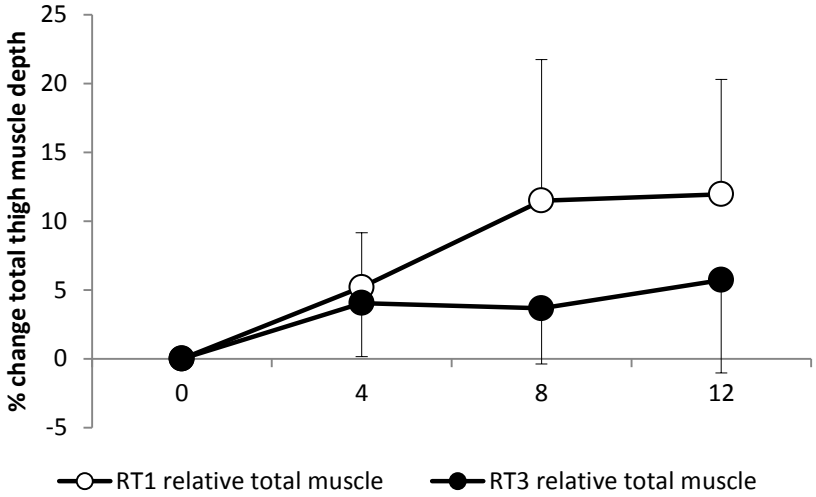
APPENDIX 1 – bi-weekly (fortnightly) and monthly (four-week) data, as absolute values, and percentage change from baseline, for all ultrasound derived measures of muscle size and architecture, and absolute values for strength measures.

TOTAL THIGH MUSCLE DEPTH AND PERCENTAGE CHANGE

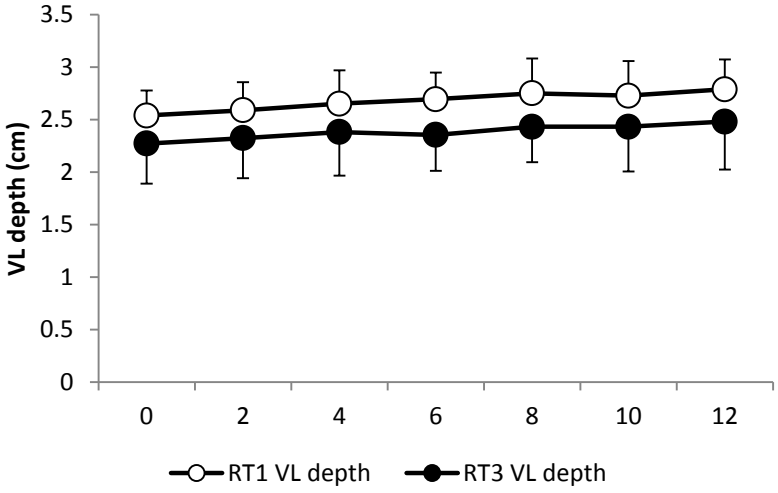


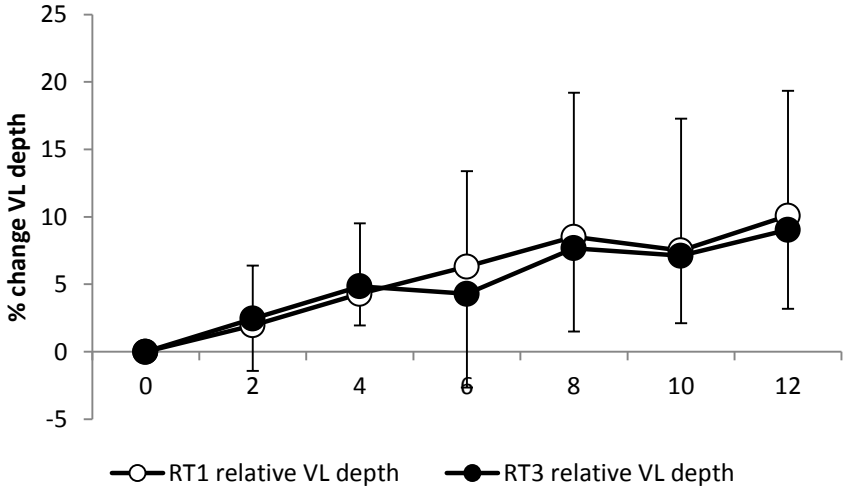


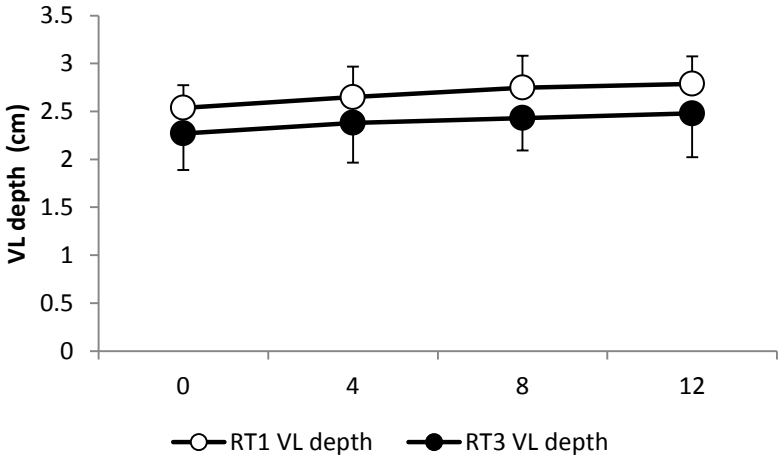


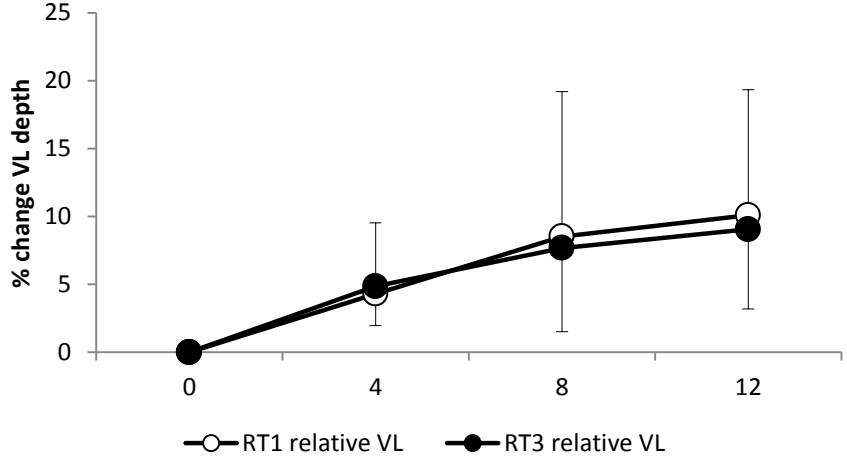


VL MUSCLE DEPTH AND PERCENTAGE CHANGE

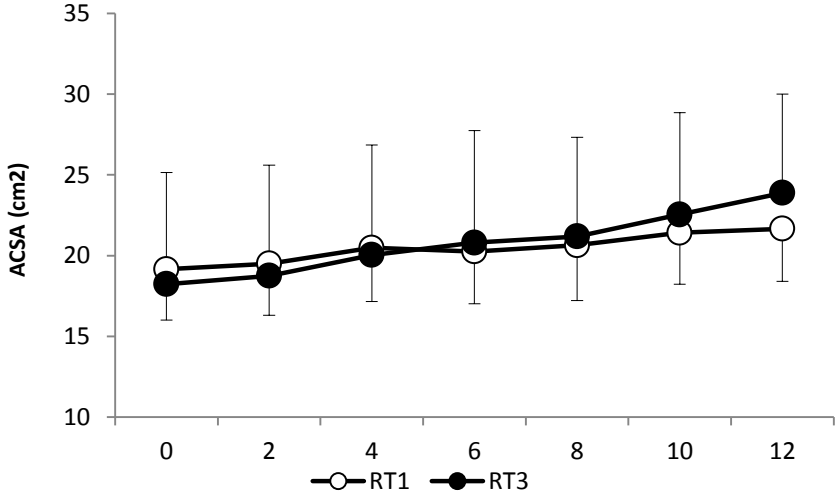


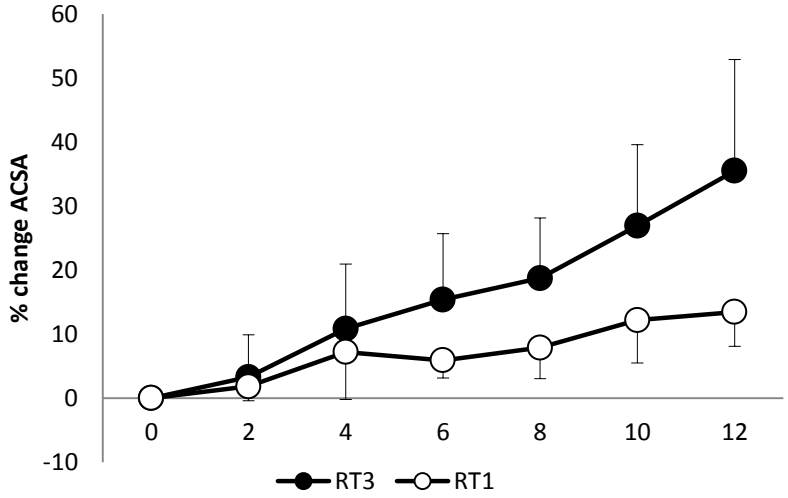


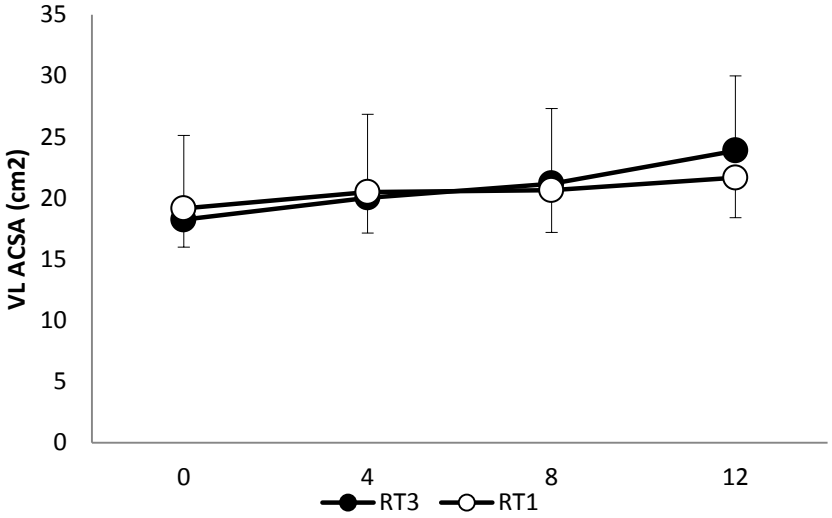


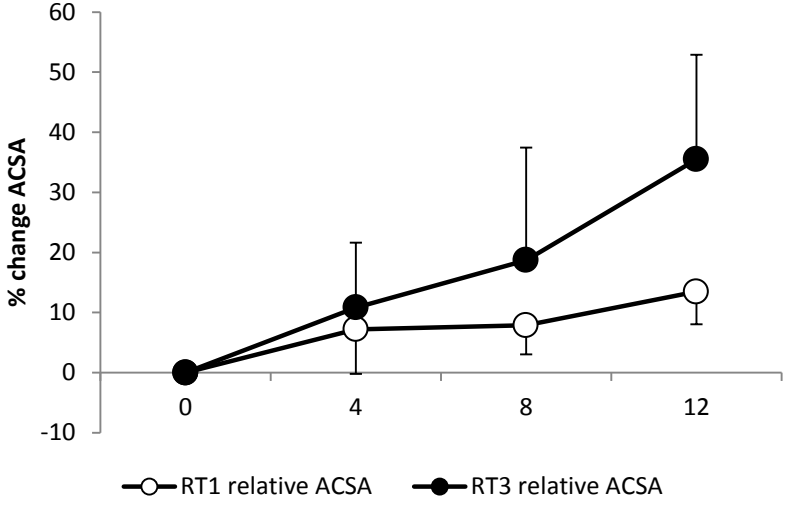


ACSA AND RELATIVE/PERCENTAGE CHANGE IN ACSA

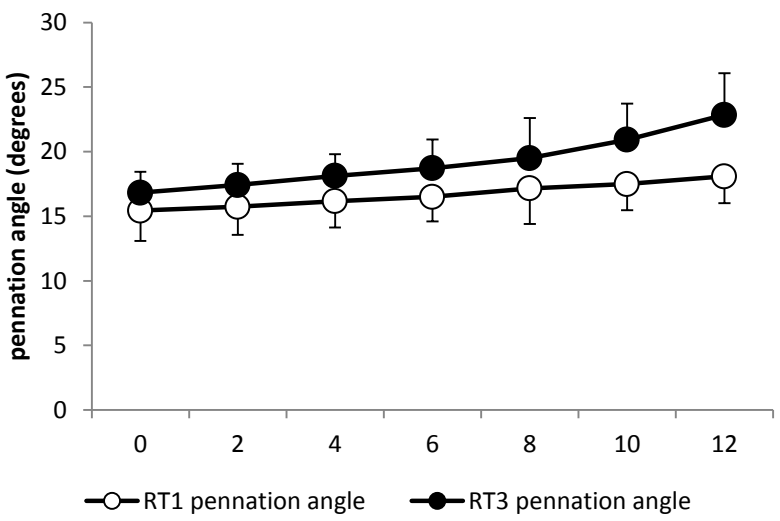


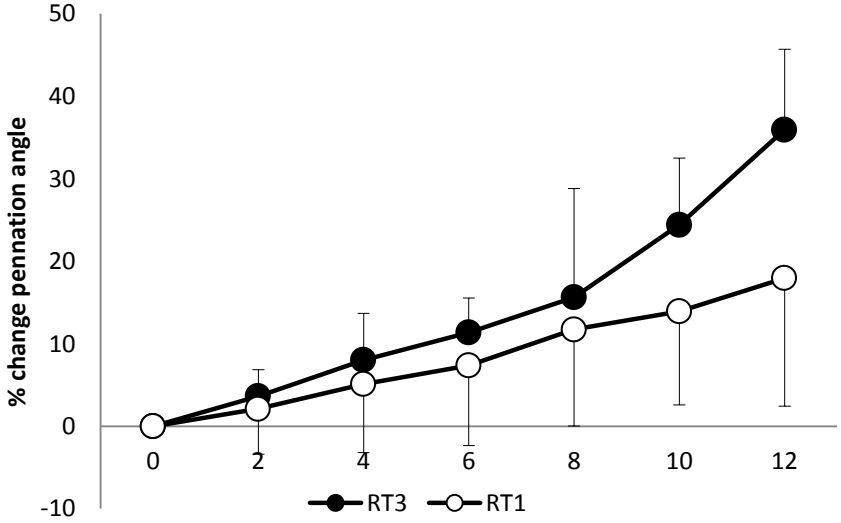


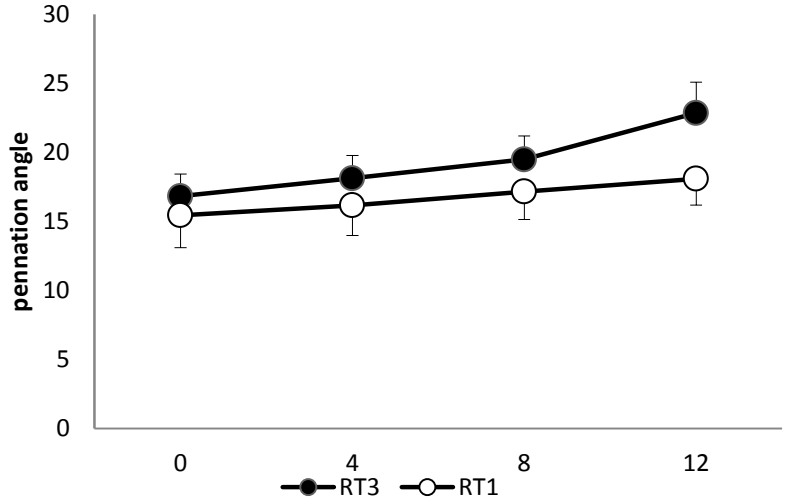


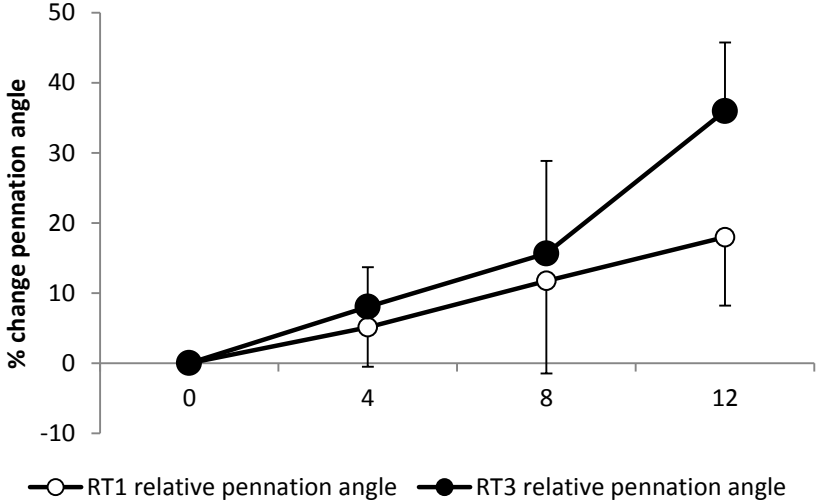


PENNATION ANGLE AND PERCENTAGE CHANGE IN PENNATION ANGLE









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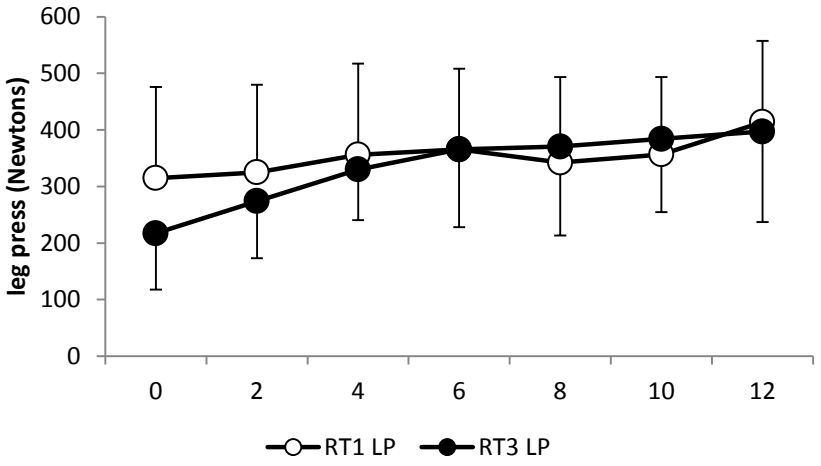

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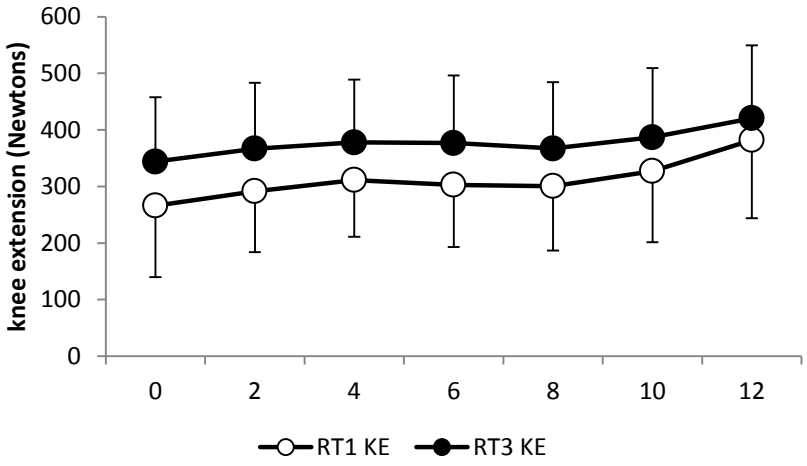
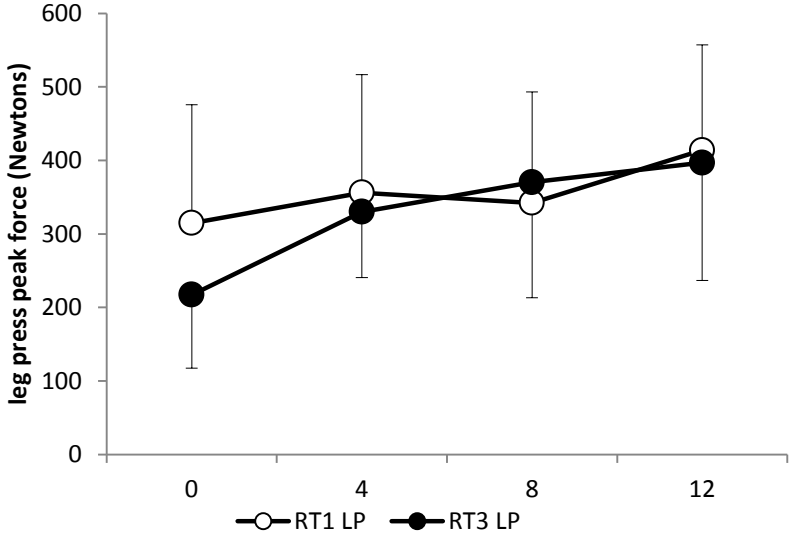
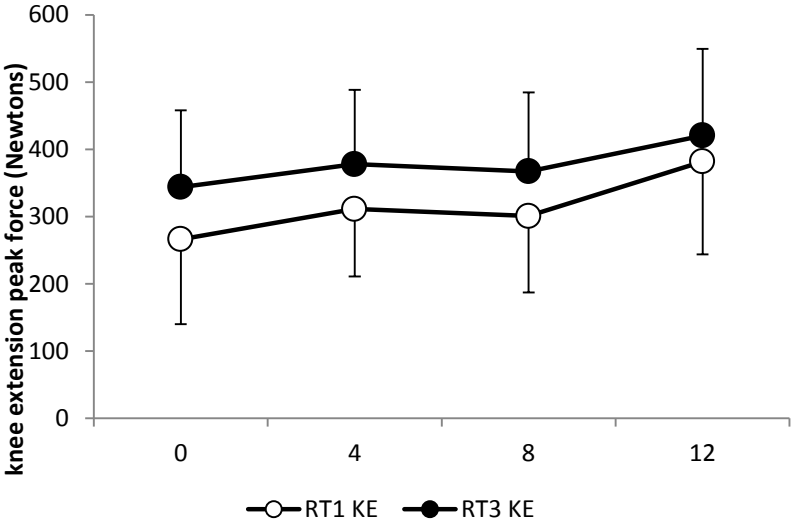
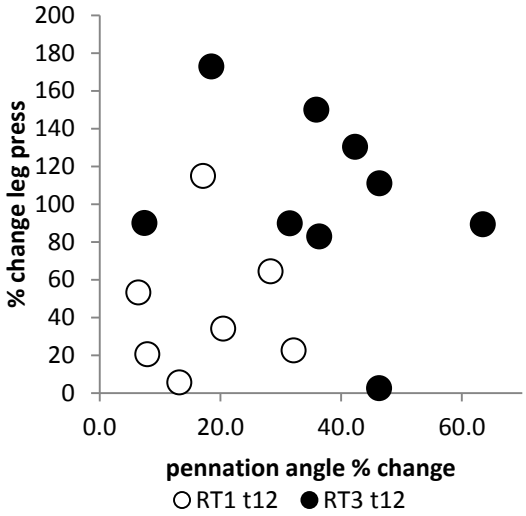


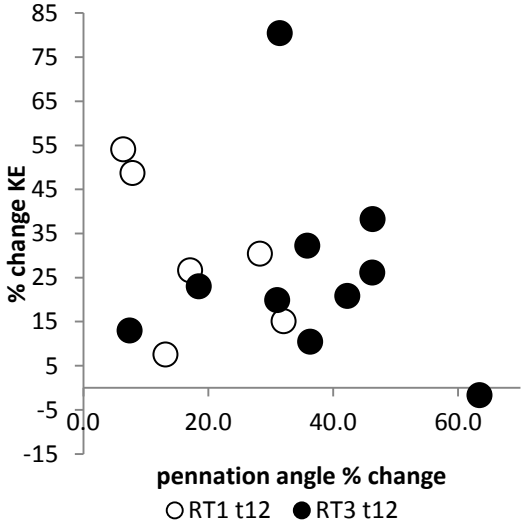


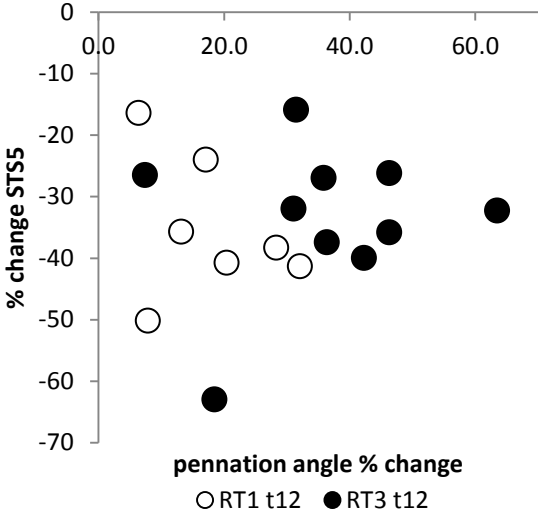


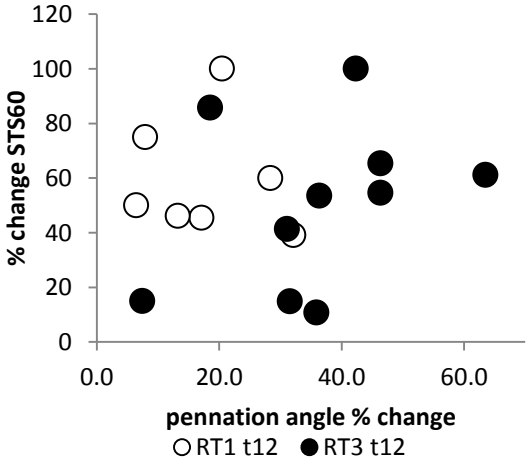
APPENDIX 2 – correlations between ultrasound derived measures of muscle mass and architecture with strength, function, and uraemic symptoms at completion of the intervention (12-weeks) by individual participants

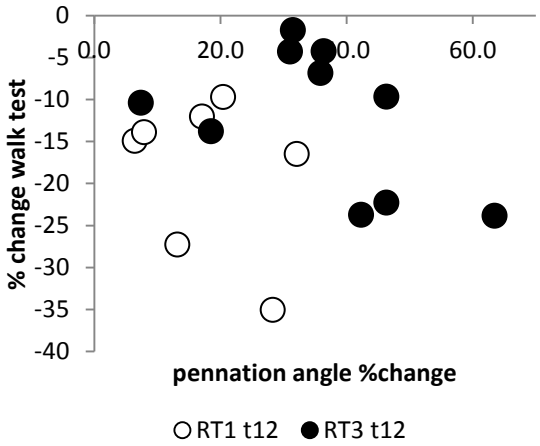
RELATIONSHIPS USING INDIVIDUAL ASSESSMENTS AT 12 WEEKS - PENNATION ANGLE

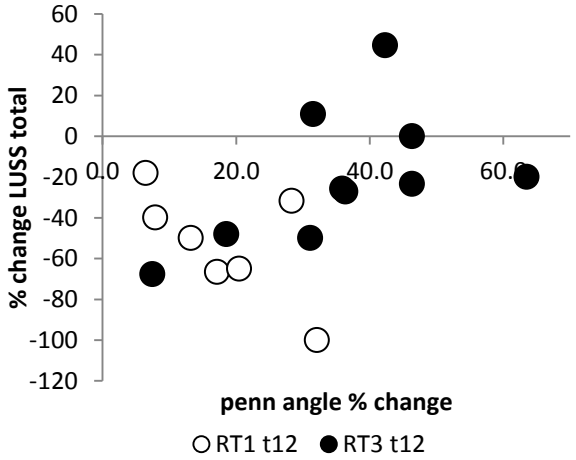




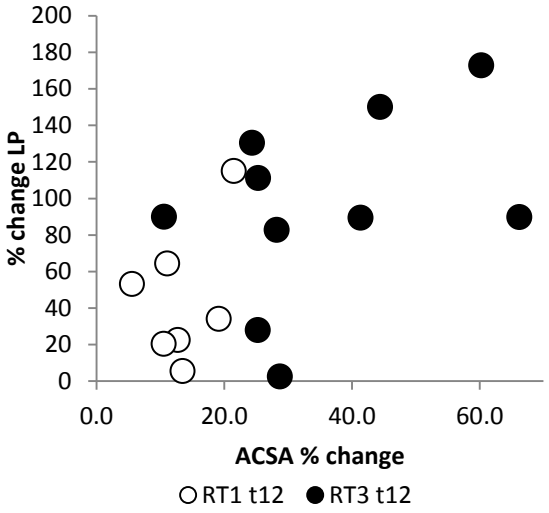


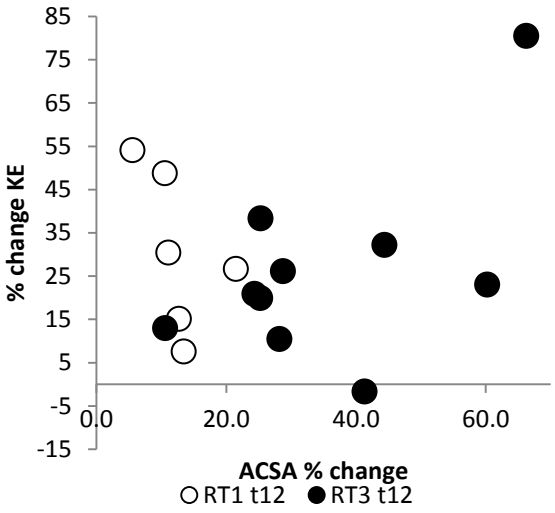


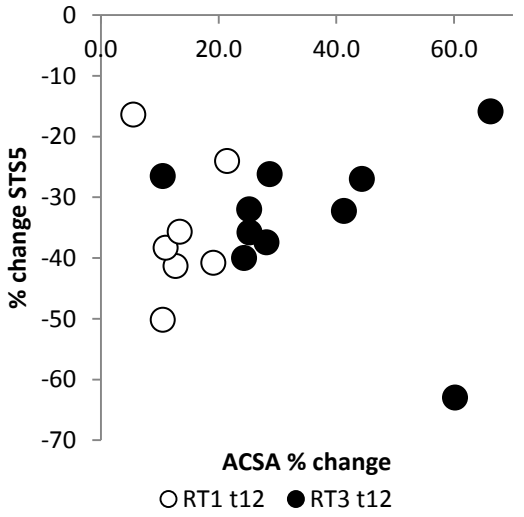


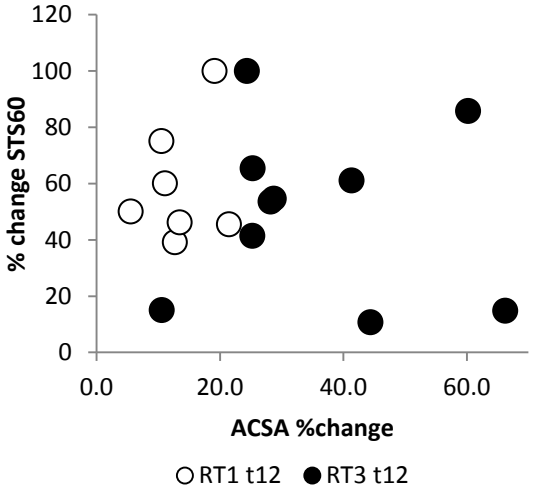


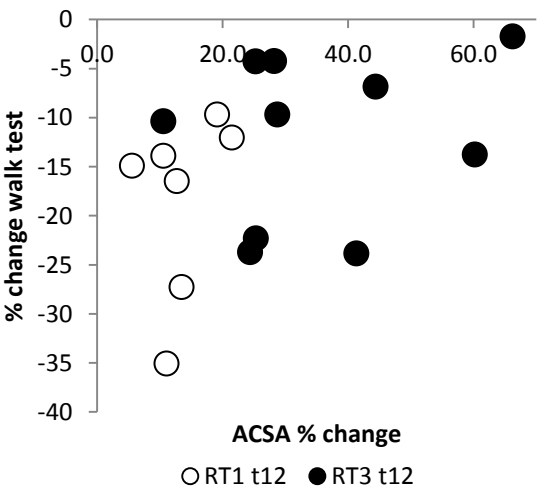
RELATIONSHIPS USING INDIVIDUAL ASSESSMENTS AT 12 WEEKS - VL ACSA

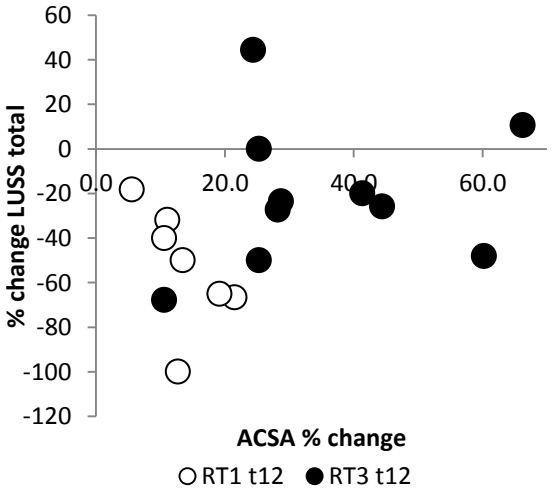




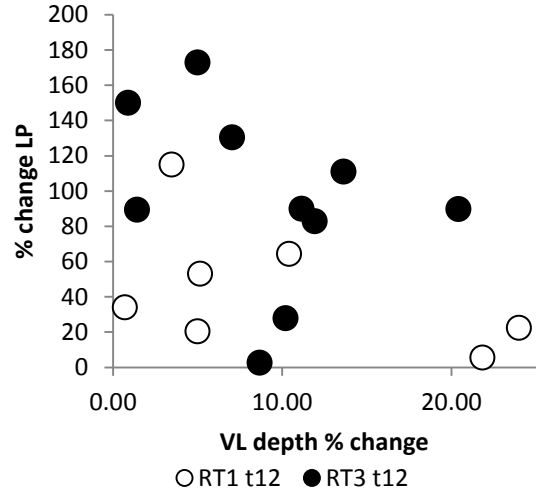


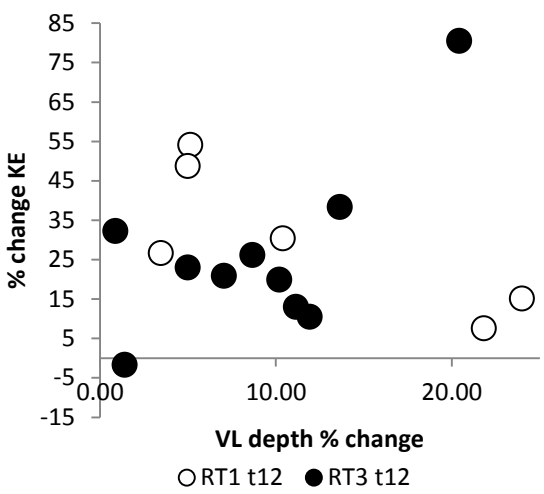


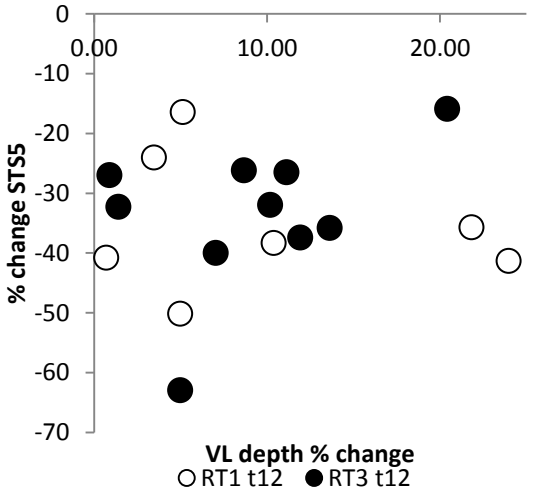


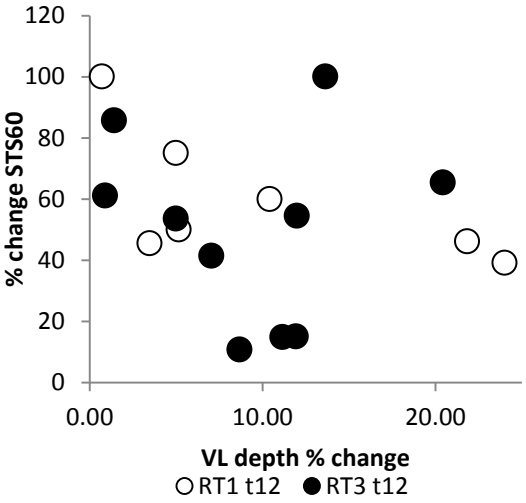


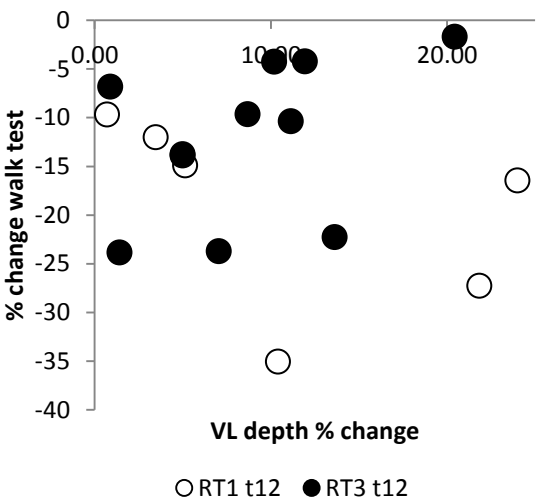
RELATIONSHIPS USING INDIVIDUAL ASSESSMENTS AT 12 WEEKS - VL DEPTH

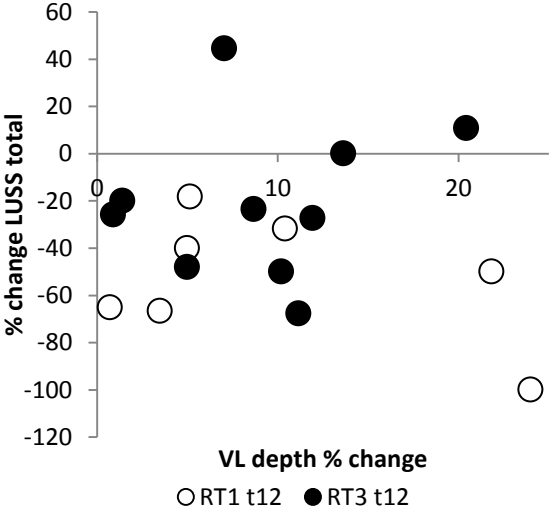






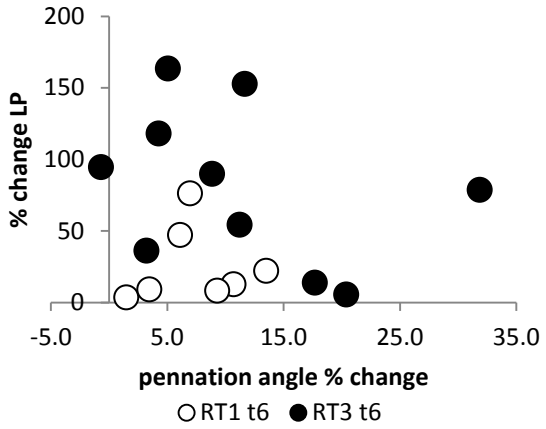


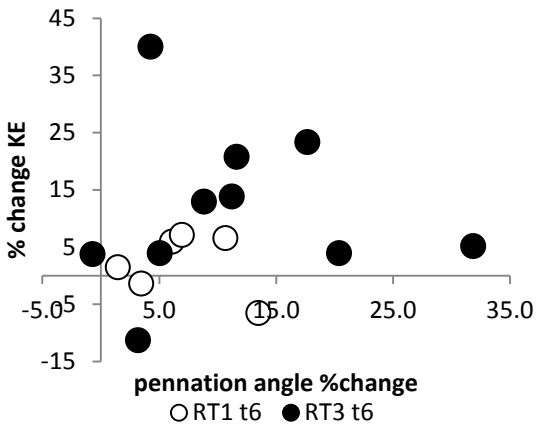


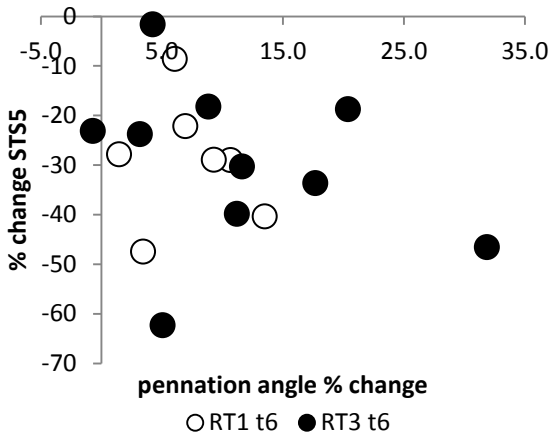


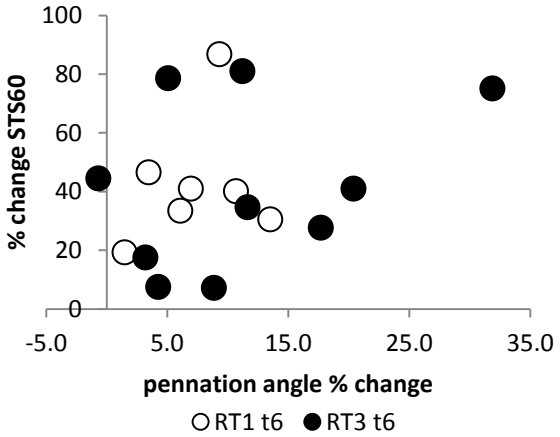
APPENDIX 3 – correlations between ultrasound derived measures of muscle mass and architecture with strength, function, and uraemic symptoms at the mid-point of the intervention (6-weeks) by individual participants

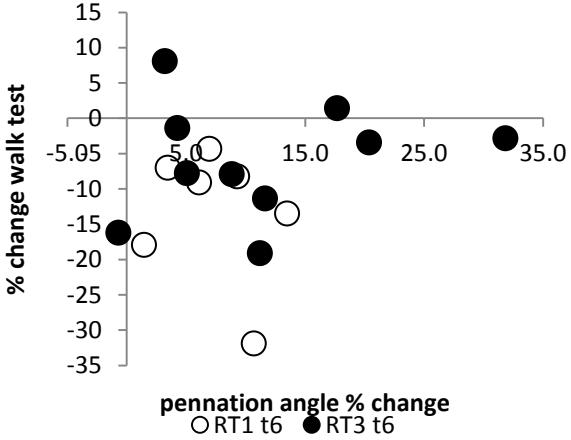
RELATIONSHIP USING INDIVIDUAL ASSESSMENTS AT 6 WKS - PENNATION ANGLE

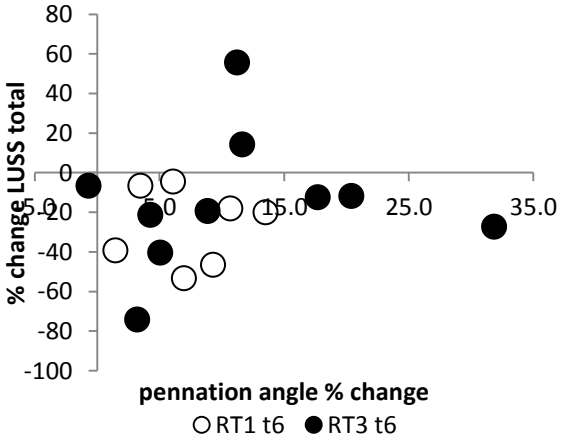




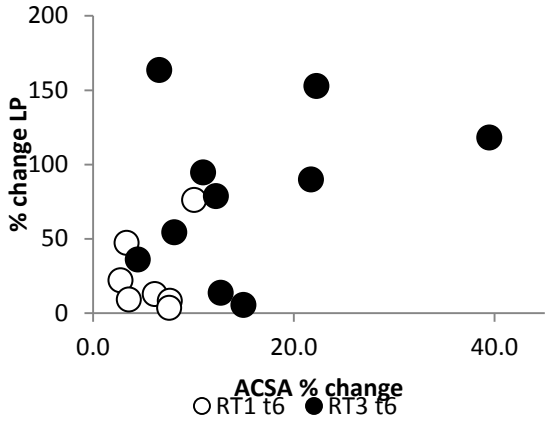


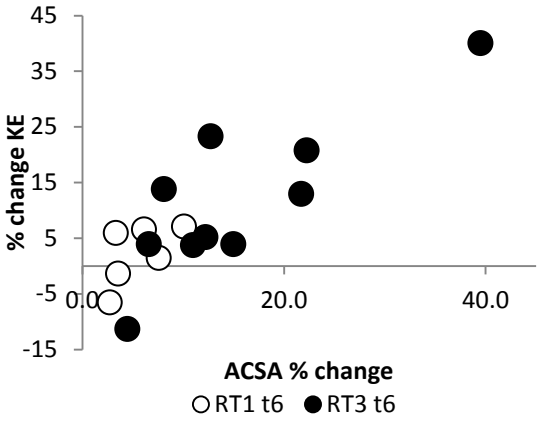


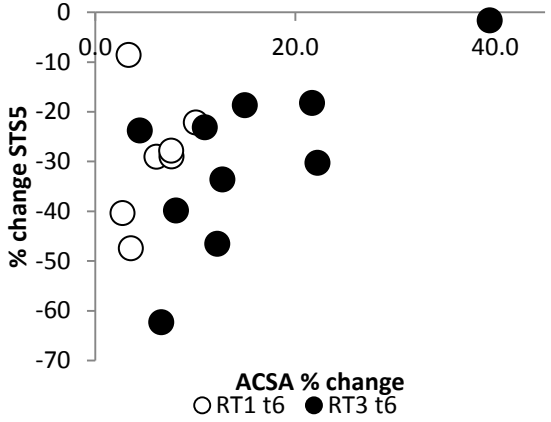


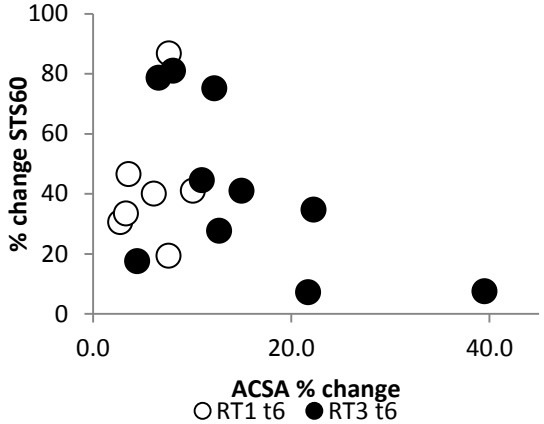


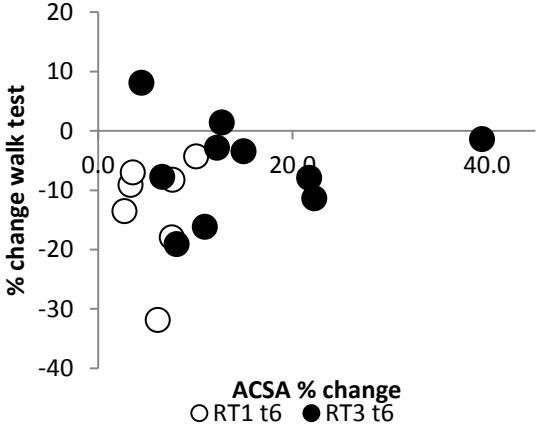
RELATIONSHIP USING INDIVIDUAL ASSESSMENTS AT 6 WKS – ACSA

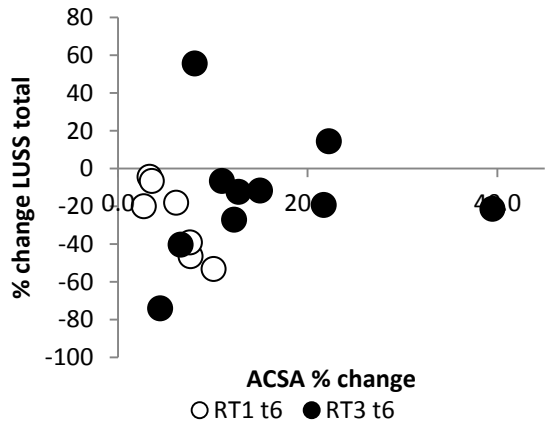












RELATIONSHIP USING INDIVIDUAL ASSESSMENTS AT 6 WKS - VL DEPTH